FOOD AND DRUG ADMINISTRATION

CENTER FOR DRUG EVALUATION AND RESEARCH

JOINT MEETING OF THE ANESTHETIC LIFE SUPPORT DRUGS ADVISORY COMMITTEE AND THE DRUG SAFETY AND RISK MANAGEMENT ADVISORY COMMITTEE

WEDNESDAY, SEPTEMBER 23, 2009

8:00 a.m. to 3:15 p.m.

Holiday Inn Gaithersburg

Two Montgomery Village Avenue

Gaithersburg, Maryland

**Anesthetic and Life Support Drugs Advisory Committee Members** *(Voting)*

**Jeffrey R. Kirsch, M.D.** ***(Acting Chair)***
Professor and Chair
Department of Anesthesiology & Peri-Operative Medicine
Oregon Health & Science University
Portland, Oregon

**Jayant K. Deshpande, M.D.**
Department of Anesthesiology
Division of Pediatric Anesthesiology
Monroe Carrell Jr. Children’s Hospital at Vanderbilt
Nashville, Tennessee

**Anesthetic and Life Support Drugs Advisory Committee Member** *(Non-voting)*

**Bartholomew J. Tortella, M.T.S., M.D.**
**Industry Representative**
Senior Director, Trauma and Critical Care Research
Novo Nordisk, Inc.
Princeton, New Jersey

**Drug Safety and Risk Management Advisory Committee Members** *(Voting)*

**Timothy S. Lesar, Pharm.D.**
Director of Pharmacy
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Albany, New York

**Allen J. Vaida, Pharm.D., FASHP**
Executive Vice President
Institute for Safe Medication Practices
Horsham, Pennsylvania

**Temporary Voting Members**

**Ed Covington, M.D.**
Chronic Pain Rehabilitation Program
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**Richard A. Denisco, M.D., M.P.H**
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**Karl Lorenz, M.D., M.S., H.S.**
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**Elaine Morrato, Dr.P.H., M.P.H., C.P.H.**
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**Martha Solonche**
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New York, New York

**Michael L. Yesenko, M.D.**
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**Julie Zito, Ph.D.**
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**FDA Center for Drug Evaluation and Research**

**Participants at the Table** *(Non-voting)*

**John K. Jenkins, M.D.**
Director, Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)
Food and Drug Administration (FDA)

**Sharon Hertz, M.D.**
Deputy Director
DAARP, CDER, FDA

**Ellen Fields, M.D., M.P.H.**
Clinical Team Leader
DAARP, CDER, FDA

**Robert Rappaport, M.D.**
Director, Division of Anesthesia, Analgesia, and
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**Henry Francis, M.D.**
Deputy Director, Office of Surveillance and Epidemiology (OSE)
CDER, FDA

**Ellen Fields, M.D., M.P.H.**
Clinical Team Leader
DAARP, CDER, FDA

I N D E X

P R O C E E D I N G S

8:00 a.m.

DR. KIRSCH: Good morning, everybody. My name is Jeff Kirsch, and I'm from Portland, Oregon. So on my clock, it says it's 5:00 a.m. But here in Washington, D.C., it's 8:00 a.m., and time to start our session.

I'd first like to remind everyone present to please silence your cell phone, if you have not done so already. I would also like to identify the FDA press contact, and if that person can stand. She's the person to contact for the press if there are any questions.

I'd like to further remind everybody that this is Swine flu season. So if you sneeze, sneeze into your arm, not into your hand. And there are hand sanitizers all over the place, so please feel free to use them so that we don't all get sick when we leave here.

Last, I'd like to let everybody know that the hotel is working on the air flow in the room, and hopefully, it will cool down soon.

Next, I'd like to go around the table and have everyone introduce themselves. We'll start over here at the FDA corner.

DR. JENKINS: Good morning. I'm John Jenkins. I'm the Director of the Office of New Drugs at FDA.

DR. RAPPAPORT: Good morning. I'm Bob Rappaport. I'm the Director of the Division of Anesthesia, Analgesia and Rheumatology Products at FDA.

DR. HERTZ: Hi, I'm Sharon Hertz. I'm Deputy Director for the Division of Anesthesia, Analgesia and Rheumatology Products.

DR. FIELDS: Hi, I'm Ellen Fields, a Clinical Team Leader in the Division of Anesthesia, Analgesia and Rheumatology Products.

DR. FRANCIS: Good morning. I'm Henry Francis, Deputy Director of the Office of Surveillance and Epidemiology.

DR. ZITO: Julia Zito, University of Maryland-Baltimore.

DR. COVINGTON: Ed Covington, Director of

the Neurological Center for Pain at Cleveland Clinic.

DR. DESHPANDE: Jay Deshpande, anesthesiology and pediatric critical care from Vanderbilt in Nashville.

DR. MARKMAN: John Markman, Director of Neuromedicine Pain Management Center, Rochester, New York, University of Rochester.

DR. LORENZ: Karl Lorenz, palliative medicine and internal medicine at the Veterans' Administration-Greater Los Angeles and UCLA.

MS. BHATT: Good morning. I'm Kalyani Bhatt. I'm the Designated Federal Official, FDA.

DR. SOLONCHE: Good morning. Martha Solonche, New York City, patient representative.

DR. DENISCO: Good morning. Richard Denisco, Medical Officer, National Institute of Drug Abuse, National Institutes of Health.

DR. MORRATO: Good morning. Elaine Morrato from Colorado School of Public Health, University of Colorado-Denver.

DR. LESAR: Timothy Lesar, Albany Medical Center, Albany, New York. I'm on the Drug Safety and

Risk Management Committee.

DR. VAIDA: Good morning. Allen Vaida, Executive Vice President at the Institute for Safe Medication Practices.

DR. YESENKO: Good morning. Michael Yesenko, patient representative.

DR. FLICK: Randall Flick, Mayo Clinic, pediatric anesthesiology, critical care.

DR. TORTELLA: Bartholomew Tortella, Novo Nordisk, industry representative.

DR. KIRSCH: A couple of microphones are still on, if you can turn them off. For topics such as those being discussed at today's meeting, there are often a variety of opinions, some of which are quite strongly held. Our goal is that today's meeting will be a fair and open forum for discussion of these issues, and that individuals can express their views without interruption. Thus, as a gentle reminder, individuals will be allowed to speak into the record only if recognized by the Chair. We look forward to a productive meeting.

In the spirit of the Federal Advisory

Committee Act and the Government in the Sunshine Act, we ask that the Advisory Committee members take care that their conversations about the topic at hand take place in the open forum of the meeting. We are aware that members of the media are anxious to speak with the FDA about these proceedings. However, FDA will refrain from discussing the details of this meeting with the media until its conclusion. Also, the Committee is reminded to please refrain from discussing the meeting topic during breaks or lunch. Thank you.

MS. BHATT: The Food and Drug Administration, FDA, is convening today's joint meeting of the Anesthetic Life Support Drugs and the Drug Safety and Risk Management Advisory Committees under the authority of the Federal Advisory Committee Act, FACA, of 1972.

With the exception of the industry representative, all members and temporary voting members of the Committees are special government employees, SGEs, or regular federal employees from other agencies, and are subject to federal conflict of

interest laws and regulations.

The following information on the status of the Committees' compliance with the federal ethics and conflict of interest laws covered by, but not limited to those found at 18 USC Section 208 and Section 712 of the Federal Food, Drug and Cosmetic Act, FD&C Act, is being provided to participants in today's meeting and to the public.

FDA has determined that members and temporary voting members of these committees are in compliance with federal ethics and conflict of interest laws. Under 18 USC Section 208, Congress has authorized FDA to grant waivers to special government employees and regular federal employees who have potential financial conflicts, when it is determined that the agency's need for a particular individual's service outweighs his or her potential financial conflict of interest.

Under Section 712 of the FD&C Act, Congress has authorized FDA to grant waivers to special government employees and regular federal employees with potential financial conflicts when necessary to

afford the Committees essential expertise.

Related to the discussion of today's meeting, members and temporary voting members of these committees have been screened for potential financial conflicts of interest of their own, as well as those imputed to them, including those of their spouse or minor children, and for purposes of 18 USC Section 208, their employers.

These interests may include investments, consulting, expert witness testimony, contracts, grants, CRADAs, teaching, speaking, writing, patents and royalties, and primary employment.

Today's agenda involves discussion of New Drug Application (NDA) 21-217, Exalgo (hydromorphone HCl), sponsored by Neuromed Pharmaceuticals, Incorporated, a modified release hydromorphone drug product indicated for the treatment of moderate to severe pain in opioid-tolerant patients. This topic is a particular matter involving specific parties.

Based on the agenda for today's meeting, all financial interests reported by the Committee members and temporary voting members, no conflict of interest

waivers have been issued in connection with this meeting.

To ensure transparency, we encourage all standing committee members and temporary voting members to disclose any public statements that they have made concerning the product at issue.

With respect to FDA's invited industry representative, we'd like to disclose that Dr. Bartholomew Tortella is participating in this meeting as a nonvoting industry representative, acting on behalf of regulated industry. Dr. Tortella's role at this meeting is to represent industry in general and not any particular company. Dr. Tortella is employed by Novo Nordisk, Incorporated.

We'd like to remind members and temporary voting members that if the discussions involve any other products or firms not already on the agenda for which an FDA participant has a personal or imputed financial interest, the participants need to exclude themselves from such involvement, and their exclusion will be noted for the record.

FDA encourages all participants, including

the sponsor's non-employee presenters, to advise the Committee of any financial relationships that they may have with the firm at issue, including consulting fees, travel expenses honoring an interest in the sponsor, including equity interests and those based upon the outcome of the meeting.

Thank you.

DR. KIRSCH: Thank you. I'd like to recognize Ellen Fields to make some opening remarks.

DR. FIELDS: Good morning.

Dr. Kirsch, members of the Anesthesia and Life Support Drugs and the Drug Safety and Risk Management Advisory Committee, invited guests, thank you for your participation in this important meeting.

Over the next two days, we will be discussing two highly potent modified release opioid drug products. Today's discussion will revolve around Neuromed's application for Exalgo, a novel modified release formulation of hydromorphone. Tomorrow, we will discuss Purdue Pharma's reformulation of their product, OxyContin, which was also the subject of a joint committee meeting in May of last year.

In contrast to product presented at joint committee meetings last year, which many of you may have attended, neither of these sponsors are seeking a tamper-resistant or abuse-deterrent claim for their formulation. However, there remain public health concerns regarding the approval of these highly potent modified release opioid products.

As Dr. Rappaport has stated at previous Advisory Committee meetings, we are faced with many difficult decisions regarding the risks and benefits of new formulations of opioid drug products due to two separate but equally important public health concerns. First, there has been a clear increase in misuse, abuse and diversion of these products occurring in the United States over recent years, and there has been a resultant increase in cases of addiction, overdose and death.

Second, while great strides have been made over the past few decades in the treatment of pain, millions of Americans have acute or chronic pain that remains undertreated, even today. Both of these problems result in significant health burdens, and it

is essential that we address how we can balance the unmet needs of patients living with inadequately treated pain, with a potential for the very treatments for that pain to be diverted, misused and abused and lead to addiction, overdose and death.

Over the past year, we have held several public meetings to discuss the problem of abuse and misuse of opioid analgesics, and the need for risk management strategies to improve prescriber knowledge about the risks for abuse, proper patient selection and monitoring, and to improve patient understanding of the importance of proper use and safe storage of opioid analgesics.

We have asked industry to prepare a risk evaluation and mitigation strategy, or REMS, to address these concerns, and we are reviewing a large amount of input from practitioners, patients, pharmacists and others. So far, a final REMS has not been established.

Neuromed has submitted a New Drug Application for Exalgo, a once-daily formulation of hydromorphone intended for the treatment of moderate

to severe pain in patients requiring an opioid analgesic over an extended period of time. Currently, the only hydromorphone available as an oral formulation in the United States is immediate release hydromorphone, indicated for the management of acute and chronic pain and dosed every four to six hours.

As you may be aware, Palladone, an extended release formulation of hydromorphone, was approved in September 2004. A meeting of the ALSDAC was held in September 2003, at which the abuse liability and options for the risk management of Palladone were discussed in detail.

Based on that data presented at that meeting documenting that hydromorphone is a highly sought after drug of abuse, and due to the fact that the dosages of the Palladone formulation were quite high, the Committee members recommended a phased marketing rollout, starting with the lowest dosage strengths, targeting specific specialties and prescribers, and incorporating monitoring of overdose or misuse in decisions on whether to expand marketing from one phase to the next.

Palladone was subsequently removed from the market in July 2005 due to findings of extensive dose dumping in the presence of alcohol.

During this meeting, you will hear presentations from Neuromed and the FDA on the efficacy and safety of Exalgo, the extent of the underlying problems of misuse and abuse of opioid analgesics, drug utilization trends for hydromorphone, data regarding the abuse liability of hydromorphone in general and Exalgo in particular, and options for the management of the risks associated with this product, including the proposed risk management plan previously put in place for Palladone.

Following these presentations, you will be asked to discuss where Exalgo lies in the spectrum of the risk for abuse compared to other opioid drug products, and based on that, where it best fits into the spectrum of risk management options. These are difficult questions, and that is why we have asked that you help us answer them.

It is also why we have sought to bring together a panel with very professional expertise to

address the challenge. Your responses to our questions, and especially your discussions that will form the foundation for those responses, will be critical to us as we consider how to approach the risk evaluation and mitigation strategy for this product.

Thank you for being willing to undertake this difficult challenge.

DR. KIRSCH: Thank you. We will now start the sponsor's presentations.

DR. WRIGHT: Dr. Kirsch, members of the Advisory Committees, FDA staff, ladies and gentlemen, good morning. I am Gene Wright, Vice President of Project Leadership at Neuromed Pharmaceuticals, a privately-held biopharmaceutical company focused on the discovery and development of pain therapies.

At Neuromed, we have a two-pronged strategy; first, to improve and enhance the effectiveness of existing therapies; and, second, to develop novel small molecule drugs that address the unmet medical needs for the treatment of pain.

We believe that Exalgo, the extended release formulation of hydromorphone designed for once-daily

administration, can become an important addition to the armamentarium for the treatment of chronic pain. Neuromed acquired U.S. development and marketing rights to Exalgo, also known as OROS hydromorphone, from ALZA Corporation in April of 2007. Our partner, Johnson & Johnson, manufactures OROS hydromorphone, and markets it in nine countries under the name Jurnista. Johnson & Johnson will also manufacture the product for U.S. sale after approval.

We recognize the benefits of hydromorphone and we also recognize its risks. This is why we've designed a REMS program called the Exalgo Alliance to ensure the appropriate access, prescribing, dispensing and use of Exalgo. It is also why we have partnered with Covidien, a leader in providing controlled pain medications for over 100 years, to commercialize the product and execute the Exalgo Alliance.

So why are we here? The overall safety and efficacy profile of hydromorphone is well-known. In our clinical program, Exalgo was found to be effective and well-tolerated when administered once a day. In our clinical pharmacology program, it was shown to

have a predictable and reproducible extended release profile.

Like with other long-acting opioids, we recognize the risks. Drs. Stemhagen and Neuman will describe the proposed REMS program, which is designed to ensure that prescribers, pharmacists and patients understand the risks, appropriate use and handling of Exalgo. When combined with our proposed REMS program, we believe the benefits of Exalgo outweigh the risks.

Now, let me explain what makes Exalgo unique. It's the patented OROS push-pull delivery system that releases medication at a constant rate. It has been in clinical use for 20 years in 13 other products, including another Schedule II product, Concerta.

As this diagram shows, the semipermeable membrane surrounding the drug and push layers of the inner core of the tablet controls the influx of water. This enables the release of the drug at a constant rate through a laser-drilled hole in the hard outer shell. The shell does not disintegrate as it passes through the GI tract, but in order to maintain its

extended release properties, it must not be crushed or chewed, because it is not an abuse-resistant product.

This unique mechanism of drug delivery allows for once-daily dosing of hydromorphone, a treatment option that is not available in the U.S. today. Over the next hour or so, we are going to review several topics with you. We will begin with a regulatory overview, and then cover our clinical pharmacology program.

Next, we'll present the safety and efficacy results of our clinical study and post-marketing safety experience. Then Dr. Lynn Webster, an expert in pain and addiction medicine, will discuss how extended release hydromorphone could add to the treatment armamentarium. Then we will discuss our proposed REMS program, the Exalgo Alliance, and provide some concluding remarks.

After our presentation, we look forward to hearing your input and taking your questions. In addition to our presenters, we have several other experts here to add to the conversation.

Now, I would like to introduce Mr. James

Ottinger, who will present our regulatory overview. Mr. Ottinger?

MR. OTTINGER: Thank you, Dr. Wright. And good morning, everyone. I'm Jim Ottinger, Vice President of Regulatory Affairs for Premier Research Group, and we represent the regulatory affairs function for the sponsor. As such, my role today will be to go over the regulatory overview of the NDA for Exalgo.

The original NDA for Exalgo, which previously was known as OROS hydromorphone, was submitted by Knoll Pharmaceuticals in December 1999. In October 2000, the FDA issued an approvable letter for this application, identifying the single clinical deficiency as the lack of a placebo controlled trial.

Now, from the period of 2001 to about 2005, there were a series of sponsor changes for the NDA, and during this time, these sponsors conducted a variety of clinical trials on OROS hydromorphone, trials that did not meet U.S. regulatory standards. We have summarized these trials in our briefing package today, but they are not the focus of the NDA

or our presentation today.

It wasn't until April 2007 that Neuromed Pharmaceuticals acquired the U.S. rights to the product, and agreed a special protocol assessment for the pivotal trial required for approval. We have completed this trial, and in a few moments, Dr. Chris Gallen will be presenting the results to you.

In August 2008, we held a pre-submission meeting with the agency to agree to the contents of the entire application. The application was resubmitted on May 22nd, and the FDA has considered this to be a complete response to the approvable letter. The application is now under active review, which brings us to this meeting today.

Meanwhile, outside the United States, in 2004, Johnson & Johnson received approval for an identical formulation to Exalgo, known as Jurnista. This product is now approved in 26 countries and sold in nine international markets. And as just noted by the FDA speaker, the regulatory history for Exalgo overlaps that of another extended release form of hydromorphone, Palladone.

Palladone was submitted in 1998 and approved in 2004. As she also noted, Palladone was withdrawn from the market less than one year after approval, due to the finding of dose dumping in the presence of alcohol. We will show you data today indicating that Exalgo is not subjected to dose dumping.

Now, I'd like to provide a brief overview of the contents of the NDA. In terms of clinical efficacy, the FDA requested one placebo controlled trial for approval. To address this, Neuromed has completed Study 301, and that study met its primary endpoint.

The safety exposure for this NDA is large, and exceeds that required for a new chemical entity; 2,335 patients have been exposed to Exalgo, with 141 treated for over one year. The clinical pharmacokinetic profile of the formulation is well characterized for a once-daily formulation and this also includes the alcohol interaction study that was mentioned previously. Dr. Wright will review the alcohol interaction data with you in the next talk.

Turning to the nonclinical data, the NDA

contains a complete toxicologic assessment of hydromorphone, including the initiation of two carcinogenicity studies. Similarly, the chemistry manufacturing control section is complete, and includes a battery of in vitro studies to assess the abuse liability of this formulation.

Last, in recognition of the potential risk associated with the use of strong opioids, the NDA contains a proposed risk evaluation and mitigation strategy. As you are all aware, the FDA has recently announced that all long-acting and extended release opioid formulations will be subject to a to-be-developed REMS. Key elements for a proposed class REMS were outlined by the agency in a Federal Register notice in April of this year.

In addition, FDA has recently approved a REMS for Onsolis, a rapid-acting fentanyl product. We agree with the FDA statements that the Onsolis REMS should not set a precedent for other types of opioids, and should be independent of the class REMS. We have considered these key developments in the creation of our REMS, which will be presented to you today as the

controlled access system called the Exalgo Alliance.

Next, I would like to review with you the proposed prescribing information included in the NDA. The proposed indication for Exalgo is identical to that previously approved for Palladone. We seek approval of Exalgo in the treatment of moderate to severe chronic pain in opioid-tolerant patients only.

The dosage range of 12 to 65 milligrams is being proposed, and that dosage range is supported by the availability of 8, 12, 16 and 32 milligram tablets. Now, you will note in our presentation today that a 64 milligram tablet strength has been developed, but we will not be marketing that strength in this country. Now, due to its proposed indication, Exalgo is contraindicated in opioid non-tolerant patients and in acute, post-operative and PRN pain.

As with all other opioids, the prescribing information warns on risk in an extensive boxed warning. Exalgo contains a warning for use in opioid-tolerant patients only, and has class labeling warnings on the risk of misuse, abuse, addiction and

diversion; a warning on the use in acute pain; the incidence and occurrence of respiratory depression; and, importantly, the boxed warning also requires that the product is to be swallowed whole and is not to be broken, chewed, crushed, dissolved or injected.

Information on the risk of injection is also contained in the warnings and precautions section. It warns that attempts to inject Exalgo for purposes of abuse and misuse may result in lethal complications. A variety of class labeling statements are also contained in this section, including a warning that the concomitant use of alcohol should be avoided.

Finally, the prescribing information contains specific language regarding the availability of the product only through the Exalgo Alliance program. This is presented as the very first item in the U.S. prescribing information, as pulled out on the slide, with more extensive text and warnings and precautions and patient counseling sections. These aspects will be covered later in the REMS presentation.

This concludes my remarks, and I know turn

the podium back to Dr. Wright to review the clinical pharmacology profile of Exalgo.

Thank you.

DR. WRIGHT: Thank you, Mr. Ottinger. Now, I will turn to the clinical pharmacology program, which characterized the pharmacokinetic and pharmacodynamics of Exalgo in 15 studies that support once-daily dosing in chronic pain patients.

This graph shows how the pharmacokinetic profile of Exalgo differs from that of the immediate release formulation. The Y-axis on this graph is hydromorphone concentration, and the X-axis is time after dosing. In this study, the currently available 8 milligram immediate release hydromorphone was given to 12 healthy subjects. It exhibited a very rapid absorption rate.

You can see how the yellow curve peaks at about one hour, followed by a rapid decline in the hydromorphone concentrations until about six hours. In contrast, we gave doses of 8, 16 and 32 milligrams of Exalgo to the same 12 subjects, and we saw substantially lower hydromorphone concentrations in

the first four hours after dosing. You can see how the rate of absorption is much slower.

This gradual increase resulted in approximately 50 percent of the peak concentrations being achieved by about six hours, leading to a broad plateau over six to 30 hours, and as expected, the concentration profiles were proportional to the dose.

This relatively flat pharmacokinetic profile suggests that Exalgo can be dosed once a day, avoiding the rapid rise sand decline of concentration seen with the currently available immediate release formulation.

Here is what the contrasting pharmacokinetic profiles look like after reaching steady-state. For this study, 29 healthy subjects received multiple doses of immediate release hydromorphone 4 milligrams every six hours, versus Exalgo 16 milligrams once daily. The total hydromorphone exposure was the same for both the immediate release and the Exalgo treatments.

The blue curve here shows the immediate release dosing over 24 hours, and as you can see, the immediate release treatment produces a markedly

fluctuation concentration profile. Exalgo dosed once daily produces a flatter profile, as shown in the green curve. The difference between these peak and trough concentrations can be quantified by a fluctuation ratio, and in this study, that ratio was 61 percent for Exalgo and it was 172 percent for the immediate release hydromorphone.

As Mr. Ottinger mentioned earlier, after the withdrawal of Palladone, all new long-acting opioid NDAs must include alcohol interaction studies. The extended release profile of Exalgo was maintained when administered with alcohol in this study of 24 subjects. In addition, an analysis of the individual data indicated that there was no evidence of dose dumping.

In this study, we gave a single 16 milligram dose of Exalgo, along with different doses of alcohol. The alcohol doses were zero, four, 20 and 40 percent, given in 240 mls of orange juice. This was designed to simulate a typical glass of beer, wine or a mixed drink. The mean hydromorphone concentration versus time curves for the fasted treatments are shown on

this slide.

Higher mean peak concentrations were achieved with the 20 percent alcohol treatment, shown in the green curve, compared to the no alcohol treatment, shown in red. But there was no greater increase in the mean peak concentrations for the 40 percent alcohol treatment, shown in the blue curve.

The main Cmax, or maximum concentration, of the 20 percent alcohol treatment was 39 percent higher than no alcohol treatment, but there was no statistically significant difference among the treatments in the area under the curve or total exposure to hydromorphone. And the difference in Cmax was less when the subjects were fed prior to receiving the alcohol.

Based on these data, we concluded that the extended release profile of Exalgo was maintained in the presence of alcohol. To further evaluate the effect of alcohol on the absorption of hydromorphone, we calculated the ratio of Cmax for the alcohol treatments versus the no alcohol treatment in each subject.

These Cmax ratio results, shown in this slide, show that the range across all treatments was 0.7 to 2.5. The greatest Cmax ratio for an individual was 2.5-fold in the 40 percent alcohol treatment group, which is highlighted in the rectangular box on this slide.

The Cmax for this patient was less than half of the dose normalized Cmax for a dose of the immediate release formulation of hydromorphone, and it occurred at six hours after the dose. So this does not meet the definition of dose dumping.

As you can see here, the profile of Exalgo with alcohol is with the range that has been reported for other approved long-acting opioids, such as OPANA ER, Kadian and Embeda. In contrast, you can see that the Palladone had a mean six-fold increase in the presence of 40 percent alcohol, and an individual increase of 16-fold, which is what led to its withdrawal.

But as we show you these data, make no mistake about our meaning. We fully recognize the risks of combining alcohol with opioids. Our

prescribing information warns against the use of Exalgo in combination with alcohol and other central nervous system depressants, because of the risk of respiratory depression, hypotension, and profound sedation that could lead to a lethal outcome. This information is also reinforced in our proposed REMS program that Drs. Stemhagen and Neuman will discuss this morning.

We are also well-aware that like any long-acting opioid, Exalgo carries the potential for abuse. In our risk evaluation program, we assessed the ways of potentially defeating the extended release mechanism of Exalgo through a comprehensive series of in vitro experiments. All of these data were submitted to the FDA and, in agreement with the agency, we are not presenting all of the details in this public forum.

However, we felt it was important to share data specifically related to the question of whether an Exalgo tablet can be chewed. Shown here are the results of an in vitro experiment regarding the force required to crush either Exalgo or OxyContin. Exalgo

is represented by the two bars on the left, and OxyContin is represented by the two bars on the right.

We tested a variety of methods. The two methods shown on this slide represent worst case scenario, indicating that the force required to crush Exalgo is four times greater than what is required to OxyContin. Also overlaid on this graph is the reported human bite force based upon the results of an independent study of 118 subjects. In these subjects, the mean maximum bite force ranged between 102 and 133 pound force, with the lowest maximum bite force being 25-pound force.

These results suggest that in this population, all subjects could crush OxyContin, but only a portion of this population could generate the bite force required to crush Exalgo. Based on these data, we think it would be unlikely to happen accidentally, given the force and the method needed to chew it. But we recognize that the risk exists. This is why we have included education and warnings not to chew the tablet as part of the label, and also the REMS program.

Another part of the risk evaluation program was an abuse liability study, shown on this slide. In this study, we compared Exalgo to immediate release hydromorphone or placebo in a single dose, single center, double blind randomized crossover design. Our subjects were opiate-experienced non-dependent recreational drug users.

This study was conducted in two phases for safety reasons. In Phase A, the subjects received an 8 milligram dose of immediate release hydromorphone as an active control. They also received an 8 milligram Exalgo dose that had been purposely altered to defeat the extended release mechanism, and they received intact Exalgo doses of 16 and 32 milligrams, as well as placebo in a crossover design. In Phase B, they, again, received the 8 milligram immediate release hydromorphone dose, and an intact Exalgo 64 milligram dose in a separate crossover.

The primary endpoint was overall drug liking, which was assessed at 10 and 48 hours after each dose. The maximum overall drug liking was the highest score for these two assessments. The

secondary endpoints included those measures listed at the bottom of this slide.

The primary endpoint, maximum overall drug liking, is shown in this graph, with the different treatments administered in both phases on the X-axis. The treatments shown in orange were administered in the first phase of the study, and the treatments shown in blue were administered in the second phase.

The results of this study give us some good news, but they also highlight the need for caution in how Exalgo is prescribed, dispensed and used. As expected, in Phase A, all of the treatments had maximum overall drug liking scores that were significantly different than placebo.

The overall drug liking scores were significantly lower with the 16 milligram Exalgo dose compared to the 8 milligram immediate release hydromorphone, while the Exalgo 16 and 32 milligram treatments were comparable to the 8 milligram immediate release hydromorphone. This makes sense when you consider how Exalgo produces an extended release pharmacokinetic profile.

Where we see cause for caution, of course, is when we look at the second bar on this graph. In this case, we intentionally altered the 8 milligram Exalgo to defeat the extended release mechanism. When we did that, it behaved like an 8 milligram immediate release dose.

For safety reasons, we didn't alter higher doses of Exalgo, but we expect that if we did alter higher doses, it would also behave like an immediate release formulation. We have addressed this risk in labeling, education, and in REMS by warning of the importance of taking Exalgo whole and not crushing or attempting to chew the tablets.

Presented here are some of the most significant risk factors for abuse and associated overdose. The potency, rate of onset, and maximum plasma concentrations are factors inherent on the molecule and the formulation. Hydromorphone is a strong opioid, with a potency and abuse liability similar to oxycodone and hydrocodone.

Rapid onset and short-acting opioids tend to reach their Cmax faster, which is associated with

increased abuse liability. Exalgo has a more gradual onset of effect. However, if Exalgo's extended release properties are defeated, the drug acts more like an immediate release formulation, providing a larger dose in a shorter amount of time.

In addition, we know that product availability correlates highly with abuse and diversion. Patient risk factors, including genetic, environmental and psychological characteristics, are also predictive of abuse potential.

Finally, prescriber experience and knowledge of responsible opioid prescribing are critical for identifying, stratifying and monitoring these known risk factors. We have designed our REMS to specifically address these risk factors through our proposed education, elements to assure safe use, and implementation plan.

In summary, Exalgo administration produces a gradual increase in plasma concentrations, achieving 50 percent of Cmax by six hours following a single dose, and peak plasma concentrations are achieved between 13 and 17 hours after dosing. Exalgo exhibits

linear pharmacokinetics, with dose proportionality over the range of 8 to 64 milligrams, and the range of mean half-life is 11 to 15 hours.

During the chronic dosing of the same total daily dose of Exalgo, administered once daily, it produced less fluctuation between peak and trough concentrations compared to the immediate release formulation administered four times a day.

As you would expect from this well-established and proven OROS delivery system, the extended release profile of Exalgo is maintained when dosed with alcohol and there is no evidence of dose dumping when administered at the same time as alcohol in healthy subjects.

The maximum overall drug liking scores in non-opioid-dependent recreational drug users for single Exalgo doses of 32 and 64 milligrams were not significantly different from the 8 milligram immediate release formulation, even though the doses were four- to eight-fold greater, but an altered Exalgo tablet would have the same impact as a corresponding immediate release dose, which we have addressed in our

label and REMS.

With these results in mind, I would now like to invite Dr. Gallen to discuss what we have learned in our clinical development program and post-marketing safety analysis.

Dr. Gallen?

DR. GALLEN: Thank you, Dr. Wright.

Good morning. I'm Dr. Christopher Gallen, CEO and Acting Chief Medical Officer of Neuromed, and I will present the clinical overview of our product.

Hydromorphone is a semisynthetic opioid first introduced into clinical practice in 1926. Exalgo, a formulation of hydromorphone intended for once-daily use, has been the subject of an extensive clinical development program, well exceeding the normal standards for a reformulation, including 15 Phase 1 clinical pharmacology studies, one adequate and well-controlled trial in opiate-tolerant patients with chronic low back pain, and 12 supportive trials in chronic pain, involving a total of 2,335 Exalgo-exposed patients.

Study 301 was a double-blind,

placebo-controlled randomized withdrawal design of the efficacy and safety of Exalgo in opiate-tolerant patients with moderate to severe chronic low back pain, not well-controlled with their prior opioids. Study 301 was designed to meet the requirements of the approvable letter with FDA, and was conducted under a special protocol assessment in order to ensure that the design and analysis were acceptable to the agency.

Following screening, patients were titrated with Exalgo at 75 percent of the equivalent level of their prior medication, and then titrated up with Exalgo either until acceptable pain relief was achieved or to a maximum of 64 milligrams of Exalgo a day.

Following titration, 266 patients were randomized to either continue at that level of Exalgo, plus rescue medication, or to be tapered down to placebo, plus rescue medication, over a two-week period, and then followed in both groups for a total of 12 weeks study duration.

As expected, the clinically important differences in discontinuation rates between the

placebo and Exalgo groups in double-blind phase with the placebo plus rescue medication exceeded Exalgo plus rescue medication in higher rates of dropout due to inadequate pain relief, rescue medication overuse, and dropouts due to opiate withdrawal, while Exalgo exceeded placebo in terms of having more adverse events. The discontinuations due to trial administrative procedures were very similar between the groups.

Per the special protocol assessment, the predefined primary outcome measure was a clinical measure -- the patient's pain score at study endpoint calculated from the patient's pain diary NRS scale during the final week of the patient's participation in the trial compared to baseline, and this was very highly significant, at a P value of 0.0001.

Similarly, the efficacy of Exalgo was evident across the range of secondary outcome measures, predefined secondary outcome measures. Subjectively, there were three measures. First, the overall pain intensity was assessed by the area under the pain intensity curve.

Second, the patient's pain was assessed at the office visit when they met with the physician. And, thirdly, there was the patient's assessment of pain and the global assessment of pain, and all were highly significant.

Behaviorally, there were two measures reflecting changes in pain sufficient to motivate an actual patient clinical decision, the decision to discontinue participation in the trial, and this was captured by the time to dropout, as well as the total number of patients who discontinued for any reason. And, again, both behavioral measures were highly significant.

Functionally, a measure assessing the impact on the medication on changing the patient's life by reducing their disability, the Roland-Morris Disability Questionnaire, was also very significant. Rescue medication use did not differ between the groups.

In summary, Exalgo was robustly effective in the relief of pain, hitting its primary endpoint and across a range of subjective, behavioral and

functional improvements in disability.

The safety profile of Exalgo in Study 301 was typical of that for strong opioids, mainly gastrointestinal, CNS and general symptoms. As one would expect, adverse event rates were higher in the titration phase than occurred in the double-blind phase after patients had accommodated to medication.

Overall compliance rates in Study 301 were typical for those of clinical trials in general, with more than 85 percent of patients at more than 80 percent compliance levels. This is consistent with the observation that the discrepancy rates between placebo and Exalgo were very similar.

Study 301 was not designed to prospectively assess diversion. For technical reasons, the drug accountability database is a tracking database that is subject to significant false positives, which are the subject of an ongoing reconciliation effort. But even accepting those false positives, it does provide a good worst case estimate of discrepancies.

So in an effort to address the understanding of the potential for diversion, and to address the

public health concerns that arise with this class of medication, we've engaged in a detailed analysis of our drug accountability database. What we found, in general, is this -- there are lower rates of discrepancy seen in the completers and in those patients who discontinue for medical-associated reasons, things like adverse events, opiate withdrawal, and inadequate pain response.

But a detailed analysis of the outlier data shows outliers in all treatment groups, and shows treatment groups that have higher rates, markedly higher rates of outliers. Specifically, 12 of the 33 patients with positive urine drug screens, two of whom were removed from the trial by the investigators as suspected diverters, showed markedly higher rates of diversion. This is consistent with the clinical literature, that patients with positive urine drug screens have a higher propensity to be potential diverters.

In addition, some of the 20 patients who reported medication as lost or stolen obviously had higher rates. By far, the biggest single group of

discrepancies arose from those patients who failed to return their blister packs, because when you fail to return your blister packs, you automatically register a discrepancy of at least 20 and as many as 56 tablets.

This group was spread across several of the discontinuation groups, and it includes all 13 patients lost to follow-up, three patients withdrew consent, one patient who reported their medication stolen, and other patients who reported medication lost. These losses may have been entirely innocent, but in light of the significant public health issue that's arisen regarding potential diversion of these compounds, have to be taken seriously, have to be considered.

We've considered these risk factors, particularly of positive urine drug screens and of poor compliance with treatments, as being clinically recognizable, and the underlying behaviors and the recognition of these underlying behaviors are addressed in the Exalgo Alliance.

Non-cancer patients in the safety analysis

encompassed almost 90 percent of the chronic pain program, but there was a significant amount of short and longer-term exposure to cancer patients. A relatively larger number of patients were studied in this program for prolonged periods in the open label safety programs.

While the majority of patients in the Exalgo program were opiate-tolerant, there was a significant amount of exposure to opiate non-tolerant patients. The vast majority of patients treated with Exalgo reported at least one adverse event. This is typical for strong opioid trials. The bulk of these drug-related adverse events were those typically expected for any opioid: GI, CNS and general administrative events.

A significant number of serious adverse events were observed, most commonly drug withdrawal syndrome, confusional state, and constipation reported in the Exalgo program. Almost all of the serious adverse events attributed by the treating physician to drug were in the minority of patients in the cancer studies, and particularly in the long-term cancer

studies.

Similarly, the vast majority of fatalities were in the cancer patients, and were overwhelmingly related to the progression of disease. The first six fatalities not related to cancer progression were thought by the investigators to be related to underlying medical issues, including infection, cardiac failure or arrest.

The seventh fatality added to this list from intentional overdose was related to a medication overdose, intentional, in our osteoarthritis Study 302, an ongoing study, and was added following the submission of the ISS.

Exalgo is actively marketed by Johnson & Johnson in nine countries under the brand name Jurnista, and is approved for the treatment of both opiate-tolerant and opiate-naive patients. Please note that Exalgo is only seeking approval for the opiate-tolerant patients in the United States.

Consistent with our target indication, while Jurnista is marketed in dosages ranging from 4 to 64 milligrams, Exalgo will only be marketed in the United

States with dosage strengths from 8 to 32 milligrams in order to maintain consistency with the upper strength level already approved in the Palladone label.

In 17 million patient days recorded between August 2006 and December of 2008, 100 serious adverse events have been recorded in the global surveillance system. Six have led to fatalities. There have been three cases of respiratory failure, all in patients over the age of 80, one with cancer, one with dementia, pneumonia and hip fracture, and one with stroke, pneumothorax, tuberculosis and a complex medical picture.

There was one case of intentional overdose, one of confusion associated with the progression of a malignant neoplasm. And outside the reporting period, there was one case of a 40-year-old man with final stage metastatic testicular cancer on 256 milligrams of OROS hydromorphone a day, plus subcutaneous morphine and haloperidol, who reportedly cracked a 64 milligram Exalgo tablet in his mouth, swallowed it and died four hours later. This was attributed by his

physician to cardiac failure due to disease progression.

Including that case, there were a total of nine cases of misuse by tablet manipulation. Three involved manipulation by medical personnel who split or cut the tablets. In the nine cases where tablets were split, crushed or pulverized, they produced no adverse event in three patients, and non-serious adverse events in six patients.

As we've just discussed, there were two cases of chewing. One was the fatality. The second was a patient on 8 milligrams of Jurnista who broke the tablet with her teeth and was hospitalized, with no adverse events reported in that record. Throughout this period, there have been no reported cases of accidental exposure in children.

In summary, Exalgo has met the regulatory requirement for a positive, well-controlled trial in opiate-tolerant patients with moderate to severe pain, while demonstrating significant improvement across a range of subjective, behavioral and disability measures.

The unique pharmacokinetic profile that supported once-a-day dosing produced a successful efficacy trial and safety profile consistent with the other strong-acting analgesics. Extensive post-marketing experience has indicated that Exalgo is safe and well-tolerated when used as directed in this population.

I'd now like to turn the microphone over to Dr. Lynn Webster, who will discuss the unmet medical need for Exalgo.

Dr. Webster?

DR. WEBSTER: Thank you, Dr. Gallen.

Good morning, everyone. As Dr. Gallen indicated, I want to address what I think are some of the unmet medical needs in our community, and where an extended release hydromorphone may provide some relief to some of our patients.

Let me begin, though, by giving you an overview kind of a perspective of some terms that are important to keep in mind. First of all, we think of pain patients as either having acute or chronic pain. Some would argue about breakthrough pain as well, but

for purposes of today, acute or chronic pain, and that we grade this by either mild, moderate or severe. These are important clinical terms as well.

Opioid tolerance is usually defined by somebody who is on 60 milligrams of morphine equivalent per day and has been on for at least a week, some people say two weeks, but these are important terms to then keep in mind.

Now, a study was conducted and published last year at the American Academy of Pain Medicine meeting, where they researched a large insurance database, where there were more than 50 million people in this database, to look at the prevalence of chronic pain and how many people were on different levels of opioids. And what they discovered from that, then, they were able to extrapolate to our national level, and they concluded, by that database and extrapolation, that there are about 45 to 50 million people in America who meet the definition of having chronic pain.

They also concluded that there were somewhere between 5.5, roughly, and 6.2 million who

were using daily opioids for the treatment of chronic moderate to severe pain, not mild, so for moderate to severe pain.

Those who met then the definition of opioid-tolerant that I had just indicated of 60 milligrams morphine equivalent per day for at least one week reduced down to about 2.2 to 2.6 million people, somewhere under three million people nationally. If the other numbers are accurate, this is how they got to that total number projected to be opioid-tolerant in the United States.

That's the population for which an extended release hydromorphone population, based upon the definitions that have been presented by the sponsor today, may find some benefit with this particular drug.

So why do we need an extended release formulation? You all know that there are plenty of them or there are several -- actually, not plenty -- but there are several on the market today. So why do we want extended release formulations? What are some of the advantages?

We know that it seems that peaks and troughs are a bit problematic with people who are experiencing severe pain. I'm going to give you a couple of examples of those in just a few moments. But if you have to take a large amount of medication very often, that can be an issue. It can create highs, lows. It can create withdrawal symptoms between the different dosings. It can actually cause significant side effects and toxicity in order to get analgesia, and then you have a trough where the patient is undertreated.

I have had patients who needed to be treated so often that they would carry around one or two days' worth of their medication, so it can be 20 or 30 pills at a time, a month’s supply can be 200 to 600 tablets. That's a large amount of medication that is available or could be available and potentially harmful to our communities. So it would be nice to see if we can smooth that out and eliminate all of that medication and that particular resource for diversion.

It is convenient, as well, to have an extended release formulation if it can provide better

analgesia or equal analgesia as a short-acting, but it is convenient for patients to be able to take once a day or twice a day.

Statistically, looking at this panel here, there's probably two to four of you who have chronic pain. Maybe one or two of you have chronic moderate to severe persistent pain. Now, if you're going to take a short-acting opioid, I've looked at the schedule today, you're probably going to have to sneak it today, because you're going to be sitting here long enough that the duration of the short-acting opioid is not going to be long enough to cover your pain.

An extended release formulation provides convenience, if not better analgesia. There certainly is some debate about that, but it certainly is convenient. And as I've said, some intra-dosing withdrawal problems. The duration of pain relief can be 12 to 24 hours with some of the extended release formulations, which are a clear advantage.

Pain is one of the -- or I should say sleep disorder is very common in patients who experience chronic pain, and if we're limited to only short-

acting opioids, it means that patients are often waking during the middle of the night to take an extra pill. And with interrupted, fragmented sleep, it's well-known now that we do not obtain restorative sleep.

So it's important to find a way that helps patients sleep throughout the night to a minimum level that they can achieve some restorative sleep. Extended release formulations offer an opportunity to help reach that end. Overall improvement in quality of life has been demonstrated in some previous studies with an extended release formulation over just immediate release or short-acting opioids.

Now, some of the reasons why we may change from one opioid to another are listed on this slide. Obviously, some medications just don't work, and I'm going to talk a little bit why morphine doesn't work for everybody, but it doesn't, and sometimes we have to rotate because we reach a side effect level with a particular opioid, and we find that if we can rotate to a different opioid, then we can achieve better pain control at lower side effect level.

Some medications seem to induce pain, a hyperanalgesic state, and if we rotate away from that to something else, we can remove that opioid-induced pain state. Tolerance is a problem with some medications, as we know, where the more we take for a period of time, it seems like it becomes less effective. It's really tied to the less effectiveness and it's due to the tolerance.

When we see patients at higher doses, usually they'll have other side effects that are problematic. So rotating away from the medications that have reached a high tolerant level, often even with the side effect problems, will allow us to overall reduce the dose and reduce the side effects associated with the opioids.

We are seeing increasingly a problem with concomitant medications affecting the metabolism of our opioids. Most opioids can be influenced -- either they can increase their level of toxicity or reduce their level of effectiveness because of the P450 state that can be interfered with with concomitant medications.

Most of our patients in chronic pain are not on just an opioid. They're on multiple medications, and many of those medications work through the P450 isoenzyme system, which ultimately could affect the blood level of our opioids 10, 20 or 30 percent.

There are multiple new opioid receptor subtypes also that make one opioid more effective for an individual than another. This is an illustration of a study that was conducted a few years ago. I believe it was a low back pain population, and the intent here was to see how many different opioids had to be tried in a population to see the maximum benefit that could be derived.

That is, could we provide -- could this population derive good pain relief from opioids, and if so, how many different opioids would have to be tried? Well, the first opioid that was chosen provided about 30 percent of the patients' relief. They added another opioid to the balance of that population, and they could add another 15 to 30 percent of that population. Then they took the balance of that population and then added a different opioid and they

could add another 15 to 30 percent.

It turns out that by the time they have tried five different opioids, that population could achieve about -- 80 percent of the population would have some pain relief, some reasonable pain relief. That's good, but it shows that we need more tools than one, and it also shows that even after five tools, five different options, five opioids, that there's still 20, maybe 30 percent of the population, and that was just with this group, that failed to get adequate pain relief.

It addresses Dr. Fields' comments earlier in the introduction that we still have an unmet need even with what we currently have available to treat chronic pain.

This is one of the reasons why we have a variance in response to our opioids. It's a beautiful slide. I think it tells us a lot. We could talk for an hour about this particular slide, for at least people knowledgeable in this field. I'm not that knowledgeable about it. But I can tell you that we have a different genetic makeup.

Each one of us has a different genetic makeup in response to an opioid. So each opioid may produce a different effect amongst each one of the panelists and everybody here in the audience and that's listening on the Web. Every one of us could respond differently to a different level of relief if we're given morphine, and this is an example where we may have a different genetic variance. Five different variances are illustrated here to the mu receptor.

So if you have two different drugs, drug one, it may work pretty well because of the height of that bar if it's a variant one; but if it's drug two, it may not, although drug one may work pretty well if you have a variant two. And there are many genetic variances of our mu receptors. Again, it's an illustration of the variability in the variance in which we respond to medications, and it's not just opioids. It's most of our medications. But clearly, this is my field and I see this clinically daily.

I have a couple of images here I want to show you of my patients. This is an unfortunate man who has had decades of severe back pain. He had tried

all conventional treatments, and he could barely get enough pain relief with very large doses of combination mediations, and eventually, I chose to implant him with an intrathecal delivery system. So that's a device that allows me to deliver medication into the spinal canal.

I found that morphine did not work and I eventually went to hydromorphone. I am now giving him intrathecal continuous hydromorphone, and it is providing him some relief. He is not Dancing with the Stars, but he is able to function today. This is one of the examples where I can say that I have experience with a continuous hydromorphone infusion, and it has provided some relief.

This is another patient of mine who had, for years, an astrocytoma that was slowly growing, and you can see where it had been eating away on her spinal cord. Believe it or not, this individual was ambulatory until just a month before she died, and she had no more visual spinal cord than what you can see here.

The lack of ambulation was not her major

problem, but her problem was pain, and it was the most intense pain I had seen in my practice. It was unrelenting. I had to give her very large amounts of combination medications.

She was receiving hydromorphone immediate release and transmucosal fentanyl -- yes, off-label, but it was the only thing that would work, and the only thing that would allow her to be able to sit and talk with her family, and even to be able to make it to see me.

Now, unfortunately, she had to take the immediate release hydromorphone every two hours, and it was probably 8 to 16 milligrams at a time towards the end, very large amount, very inconvenient, but it was the only thing that she could do or I could provide her that made her life bearable.

Then another example of an individual who had a trivial ankle injury a few years ago, right lower extremity, bumped his ankle in a store, developed complex regional pain syndrome, and this is the consequences of that. He tried -- we tried a number of different medications, multiple

interventions, and really none of the current medications helped him that were taken orally or transdermally. He eventually did proceed to have an intrathecal delivery system and is doing better with an intrathecal source of medication.

Now, I've just given you three dramatic, if you will, examples of patients who suffer a great deal and I have had to go to extremes to provide them relief. It's good for dramatization.

The truth is that there are hundreds of my patients out there that are not as dramatic, that do not get very good pain control, and we need more tools in our toolbox. We need more variety in the way in which we can deliver these medications so that we can provide them the relief and some dignity in their life.

Extended relief hydromorphone, in summary, then, as you all know, has widely been accepted and it has actually been presented already. It is an effective short-acting analgesic. Hydromorphone is not significantly metabolized by the cytochrome P450 system, and that's unique among the opioids. So it

provides us a unique option, where others may be influenced by all of the other medications that we provide that could increase their toxicity or lower their effectiveness.

And hydromorphone has been used effectively, as I say, in prolonged continuous infusions intravenously, but also intrathecally, and I have that personal experience.

So I believe an extended release hydromorphone formulation could help me provide pain relief to a subset of my population. Thank you very much.

I'm now going to introduce Dr. Stemhagen.

DR. STEMHAGEN: Thank you, Dr. Webster. Good morning. I'm Annette Stemhagen. I'm Senior Vice President of Epidemiology and Risk Management at United BioSource Corporation. We've been assisting Neuromed and Covidien in the design and implementation of the Exalgo Alliance REMS program.

We've designed the program with features already in use in numerous other risk management programs across a wide variety of therapeutic areas,

and also looking at the elements that the FDA outlined in the April Federal Register regarding long-acting opioids. We're confident that it will help ensure proper distribution, prescribing, dispensing and use of Exalgo.

The first step in developing an effective REMS is to identify the risks to be mitigated and the strategies to use. As with other opioids, the primary risks that Exalgo Alliance will address are overdose, abuse and diversion.

Dr. Wright earlier referred to risk factors we need to consider when mitigating risks. Those that put patient at risk for opioid overdose are included on this slide -- non-opioid tolerance, general health status and co-morbidities, patient demographics, and concomitant medications and alcohol.

There are also known factors that can indicate a risk of abusing an opioid. These include personal history of things like substance or sexual abuse, having a mental disease, age groups, and being under significant psychological stress.

It's important that health care

professionals recognize these factors and take them into account when initiating a therapy with an opioid.

Now, to talk about diversion. About 90 percent of the time, the primary source of nonmedical use of opioids is from the patient. As shown in this slide, 55.7 percent of abusers obtained the opioid free from a patient that was a friend of relative; 14.8 percent bought or stole it from that patient who was a friend or relative; and, about in 19 percent, the abuser was the patient who obtained it from one single physician. It's impo+rtant to understand then that the vast amount of diversion is not from doctor shopping or through the Internet.

In order to minimize these risks and to address the risk factors that I just talked about, the REMS is designed to meet these goals. Prescribers, pharmacists and patients should understand Exalgo risks, as well as responsible prescribing and use. Exalgo should only be used in opioid-tolerant patients. Overdose of Exalgo should not occur. Abuse and diversion of Exalgo should not occur. And unintended or accidental exposure of Exalgo should not

occur.

The REMS is designed so that it will not impede the ability of appropriate patients to receive Exalgo, while reducing the risks of overdose, abuse and diversion.

Exalgo will reach the goals of minimizing risks by creating an alliance, strengthening communication between prescribers, pharmacists and patients, focused on the factors that I just reviewed. Exalgo can only be prescribed by enrolled health care professionals who acknowledge understanding of opioid risks and responsible prescribing and use.

Exalgo can only be used by enrolled patients who acknowledge understanding of opioid risks and responsible handling and use. And Exalgo can only be dispensed by enrolled pharmacies and health care settings that acknowledge understanding of Exalgo risks and responsible dispensing and use.

To support this responsible prescribing, dispensing and use, our REMS program intervenes at the levels of those key stakeholders I just mentioned -- prescriber, pharmacist and patient. Primary risk

factors for opioid overdose and abuse are incorporated into the stakeholder education, with messages about proper patient selection, dosing administration, patient education, and the importance of counseling on safe use and handling.

The Exalgo Alliance also focuses on the risk of nonmedical use of Exalgo and the need for proper handling, storage and disposal. These include messages that giving or selling Exalgo is illegal, and that Exalgo must be kept in a secure location and protected from theft.

The REMS supports this process through four critical aspects of risk mitigation -- education and counseling, controlled access, surveillance and monitoring, and continuous program improvement. Education and counseling will occur through a communication plan that addresses the risks and benefits. Health care professionals will be instructed to counsel patients about Exalgo risks.

Much of the Exalgo Alliance is directed to improving the patient care paradigm by encouraging, or in fact, requiring interaction between the prescriber

and the patient regarding safe product use. Controlled access means that only those prescribers, pharmacies and patients who acknowledge understanding and agree to follow Exalgo Alliance will be able to receive Exalgo.

Covidien also plans a careful and comprehensive assessment program to evaluate the REMS and its effectiveness, and to make adjustments as necessary.

I'm showing here the components of the REMS and you'll see this language. I know FDA is going to speak to you later about REMS in general. These are sort of terminologies unique to REMS; professional labeling, a medication guide, a communication plan, elements to assure safe use, an implementation system, and as noted, assessment, with continuous program improvement.

The foundation of any risk management program is professional labeling. The professional labeling informs the health care professional about the risks of Exalgo and how to responsibly prescribe and dispense.

As you saw earlier, the prescribing information includes key information in a black box warning that covers Exalgo risks, appropriate patient selection, and safe use procedures for mitigating the risks of overdose, abuse and diversion.

The prescribing information also provides specific instructions on the Exalgo Alliance program, including its rationale and the processes such as stakeholder enrollment and prescription verification.

The REMS information is reinforced to the pharmacist on the package labeling, with instructions that he or she must verify prescription eligibility, be sure to dispense only to opioid-tolerant patients, provide a medication guide with each dispensing, and counsel the patient. There are also instructions for the pharmacist to use when counseling patients.

Exalgo is for once-daily use. Tablets should be swallowed whole and not broken, crushed or chewed. And Exalgo should be dispensed in a child-proof container, with directions to keep out of the reach of children.

A medication guide for patients is also a

key educational tool. The pharmacist must give this to the patient with each dispensing. It reminds the patient how to safely use and handle Exalgo, and it reinforces what they learned from their prescriber when they enrolled in the Exalgo Alliance program.

The medication guide is written in patient-friendly language at an appropriate reading level. Here are some of the specific messages that it provides. It must be kept in a safe place away from children. Exalgo must be protected from theft or abuse at home and at work. An overdose can cause life-threatening breathing problems that can lead to death if you are opioid not-tolerant, if you do not use it exactly as prescribed, or if you do not swallow it whole.

The core messages provided in the labeling are carried throughout the program through the communication plan. This ensures that messages are heard frequently and consistently whenever a stakeholder interacts with Exalgo. The communication plan is a REMS element that directs education and outreach to health care professionals and to their

patients through their health care professional.

The communication plan includes a number of educational materials, as listed here. One key piece is the prescriber-patient medication agreement, or PPMA, that I will describe a little bit later. You will see that there are messages throughout the prescriber, patient and pharmacist.

Core communication regarding overdose, abuse and diversion are shown here. These messages are continuously emphasized throughout the educational materials for all stakeholder groups, and are in the elements to assure safe use. The messages reinforce proper patient selection and monitoring, safe use of the product, and prevention of accidental overdose, exposure and diversion.

Another method of communicating REMS materials and messages is the Exalgoalliance.com Website. The Website will be available at the time of Exalgo approval and used for all REMS functions. It contains educational materials, as well as enrollment forms and tools.

Exalgo Alliance will provide a resource

center on the Website, with tools or links to tools that prescribers can use in making a decision whether a patient is a good candidate for Exalgo prescription. This includes tools such as the opioid risk tool, or ORT.

Another element of the communication plan is an educational slide module for prescribers. For example, here is one slide from that module that includes messages for proper patient selection and how to identify the right patient for Exalgo treatment.

Appropriate patients are those who are opioid-tolerant, have moderate to severe pain, and require continuous around-the-clock analgesia. There is also a reminder that Exalgo is a Schedule II product containing hydromorphone that can be abused or diverted, and that care must be taken in selecting the correct patients for Exalgo treatment.

Moving now to elements to assure safe use, Exalgo Alliance will control access to Exalgo by requiring that stakeholders become educated on the risks of Exalgo and on responsible prescribing, dispensing and use prior to initiating therapy and

throughout therapy. Through this effort, health care professionals must initiate patient interactions, thus providing a higher level of care than might customarily occur.

Exalgo Alliance includes five elements to assure safe use. First, Exalgo can only be successfully prescribed by health care professionals authorized to prescribe Schedule II drugs and who are enrolled in the program, after having acknowledged understanding of Exalgo risks and responsible prescribing and use.

Second, Exalgo can only be used to treat patients who have signed the PPMA agreement with their prescriber, acknowledging they understand the risks, and will adhere to responsible use and handling and who are enrolled in Exalgo Alliance.

Third, Exalgo can only be dispensed by pharmacies and other health care settings authorized to dispense Schedule II drugs, and that are enrolled in Exalgo Alliance and have acknowledged their understanding of the risks and agreed to responsible dispensing and use.

Four, pharmacies must obtain verification of prescription eligibility prior to each Exalgo dispensing. And, finally, distributors must agree to sell only to enrolled pharmacies and health care settings.

As I mentioned before, one of the primary tools to assure that patients follow safe use conditions is the prescriber-patient medication agreement, or PPMA. The prescriber will review this document with the patient in order to be sure that the patient understands appropriate use prior to initiating therapy. They will then both sign the agreement, and a copy will be kept in the patient's chart.

In reading this, the patient must acknowledge reading the medication guide, that their physician has explained Exalgo's risks and benefits, the concept of opioid tolerance has been explained and understood, the reasons for Exalgo use are understood, meaning the indications, and the agreement also emphasizes that Exalgo must be kept in a safe place and away from children or from anyone for whom it is

not prescribed.

This is a very significant element of the REMS that will improve patient care by requiring an interaction between the patient and his or her prescriber.

Now, when creating a REMS, it's important to test the education and communication materials before they are implemented, not only to determine if the messages are clear, concise and easy to understand, but also to obtain stakeholder reactions to the program requirements.

To do this, we conducted a serious of qualitative and quantitative evaluations with prescribers, pharmacists and patients of the core Exalgo Alliance elements. The purpose was whether they understood the risks and benefits and safe use and handling of Exalgo, to uncover if any information was missing, and to elicit comments for how the material might be improved to enhance retention and communication of necessary materials.

The education and enrollment materials that were tested are shown here. Key materials included

the medication guide and the PPMA and the enrollment materials. The numbers of stakeholders who participated in these surveys, these were unique samples for qualitative and quantitative testing, are shown here.

The sample included a wide distribution of physician specialties, those with significant experience treating chronic pain, and is representative of the prescribers that will be the focus of Covidien's commercialization efforts. Physicians were oncologists, physiatrists, anesthesiologists, and those specializing in pain medicine. Pharmacists were both from independent and chain pharmacies, and there were a substantial number of patients with chronic pain.

Our testing found that more than 90 percent of all key stakeholders interviewed understood the Exalgo Alliance. Based on our testing, we found that the stakeholders understood the risks. Additionally, they understood their responsibilities and roles in participating in Exalgo Alliance when it is used in actual practice.

We believe that if they read the materials, they will understand them. Exalgo Alliance is a program to ensure that these documents are read and discussed.

You can see here that stakeholders expressed willingness to participate in the program at high levels. We also identified several gaps in the materials, and modifications have been proposed to the medication guide, the PPMA, and the enrollment forms.

Based on these results, we're confident that we have the right elements in place to assure safe use of Exalgo through the Exalgo Alliance. We've designed a rational and responsible REMS that will maximize the benefit-risk profile, while not imposing undue burden on the key stakeholders.

Now, Dr. Neuman will discuss how Covidien will implement this program, and the procedures that we've put in place to assure its success.

DR. NEUMAN: Thank you, Dr. Stemhagen.

Good morning. My name is Dr. Herbert Neuman, and I'm Vice President of Medical Affairs, and the Chief Medical Officer for Covidien

Pharmaceuticals. In my role as Chief Medical Officer, I will lead the team that will be responsible for implementing and maintaining the Exalgo Alliance.

In order to fully understand the Exalgo Alliance, I believe you have to understand a little bit about Covidien. We're a global health care company, and our pharmaceutical subsidiary, Mallinckrodt, Incorporated, which is where I work, has been an active producer of opioid analgesics since 1898.

Exalgo builds upon our existing foundation of safety, surveillance and monitoring that we use across all of our products. We want you to know that Covidien will be a responsible steward of Exalgo and the Exalgo Alliance.

So what do we mean by responsible stewardship? Well, at Covidien, we've broken it down into four key components -- responsible commercialization, responsible distribution, a rational and achievable REMS, and open communication with governmental and scientific communities.

Responsible commercialization for a product

like Exalgo means directing our marketing and sales efforts toward the appropriate education and enrollment of experienced pain practitioners. These are prescribers who have a history of prescribing multiple long-acting opioid analgesics.

By focusing on the most experienced few percent of DEA registrants, we believe we've identified a group of prescribers, when working within the Exalgo Alliance, who are most likely to safely and effectively use Exalgo. We are expressly not going to be marketing direct to consumers.

All relevant Covidien employees, from the sales force through the executive team, are required to support REMS activities. In addition, all our employees must adhere to pharma guidelines, as well as our own Covidien SOPs that deal with appropriate interactions with prescribers. Throughout our company, we have a zero tolerance policy for infractions against these guidelines or our SOPs.

Responsible distribution involves our long-term relationship with select distributors who have broad and deep experience in handling controlled

substances. The distributors will be contractually prohibited from delivering Exalgo to non-enrolled pharmacies. We routinely audit our distributors, and this prohibition will be part of our audit plan going forward.

The Exalgo Alliance work flow is designed to be compatible with existing stakeholder processes. A responsible REMS is really the key to the safe use of Exalgo. As you heard from Dr. Stemhagen, the Exalgo Alliance was designed to minimize the risk of overdose, abuse and diversion. It specifically addresses the known risk factors for overdose and abuse, and targets the primary source of diversion, over 80 to 90 percent of which is not related to street level dealing or organized crime.

That is why the educational component of the Exalgo Alliance is so important. We repeatedly educate prescribers, patients and pharmacists around the need to protect Exalgo from this type of diversion. Focusing education on the primary source of diversion is part of a responsible REMS.

And the Exalgo Alliance is flexible. It is

designed to adapt to changes in the art and science of risk management or changes in the regulatory environment. As a class-wide REMS for long-acting opioids is finalized, we are ready to adapt the Exalgo Alliance to fit that new standard.

The implementation of the REMS is equally important. The primary goal is to ensure appropriate patients have access, and the implementation is really a balance between access and safety. The system was designed to detect deviations from the program. If a deviation occurs, we will aggressively address it, and I'll talk more about that in a moment.

If, in the operation of the Exalgo Alliance, we come across information that suggests illegal activity, we will forward this information to relevant law enforcement authorities. And there is an opportunity to responsibly use de-identified data to better understand the behaviors of key stakeholders within the alliance.

The bottom line is the alliance will allow patient access while ensuring safe use procedures have been implemented. The implementation system is the

infrastructure that supports the elements to ensure safe use. The core of the implementation system is the Exalgo Alliance database.

This overview walks you through the implementation process, starting with the prescriber who enrolls in the Exalgo Alliance. The prescriber then educates and reviews the risks and benefits of Exalgo with the patient within the context of a prescriber-patient medication agreement. The patient is then enrolled in the Exalgo Alliance.

The patient presents a valid prescription and a PIN to the pharmacist, who verifies that the prescriber and the patient are enrolled in the alliance, reviews the medication guide with the patient, and then dispenses Exalgo.

A screen shot of the Exalgoalliance.com Website. On this Website, all of the enrollment procedures can take place. A prescription can be validated by a pharmacist, and any stakeholder can download electronic versions of forms or tools that are relevant to them.

As you've heard, the Exalgo Alliance is a

controlled access system. This graphic displays both the product flow of Exalgo, starting from Covidien through the distributors, ultimately going to the patient, but it also highlights the interactions the various stakeholders have with the Alliance.

The Exalgo Alliance system links the prescriber, patient and pharmacy to verify completion of safe use procedures. For example, if a patient is not enrolled in the system, the pharmacist will receive a do not dispense message.

If the system detects deviations, they will be addressed by a corrective action. Many can be addressed by communicating to the specific stakeholder. For more serious deviations, there is an escalation procedure. The initial corrective action involves reeducating the stakeholder on the Exalgo Alliance policies and procedures. Further deviations will result in termination from the Exalgo Alliance until the matter can be reviewed and a decision made by Covidien whether or not to offer re-education and reenrollment.

The guiding principle for the Exalgo

Alliance is this -- if a prescriber, pharmacist or patient is unable or unwilling to stay within the guidelines of the Exalgo Alliance, we do not want them prescribing, dispensing or ingesting Exalgo.

It is critical to the success of any REMS that it continually be evaluated and improved as necessary. The Exalgo Alliance has an extensive evaluation program that includes performance, surveillance and signal detection. Assessment reports will be sent to the FDA annually for the first three years, and again at years five and seven after REMS approval.

I've outlined some assessment activities on this slide. We've designed program performance metrics that make up the core assessment. These include number of prescribers, patients, pharmacists enrolled, as well as a comparison of the number of prescriptions presented to the pharmacy versus the number of prescriptions actually dispensed.

We will also be doing prospective surveys and studies, including knowledge, attitude and behavior surveys. And we intend to use external

claims databases to help identify underlying characteristics of the patients who receive Exalgo.

The safety assessment of Exalgo has three parts -- the Exalgo Alliance implementation database, which you've heard a lot of; Covidien's pharmacovigilance activities; and the Covidien group that's responsible for surveillance and monitoring. Together, these resources are used to monitor the benefit-risk equation for Exalgo.

The Exalgo Alliance uses a variety of information sources in its surveillance process. Each of the three primary risks has associated surveillance tools and activities. Many of them may be familiar to you and are commonly used in other risk management plans.

There is a defined intervention process for surveillance and signal detection. If a signal is detected, the Covidien risk management function, in conjunction with pharmacovigilance and biostatistics, works to investigate and verify the signal. If a signal is validated, the risk management oversight committee, a multidisciplinary group of Covidien

employees, evaluate the signal and recommend appropriate action. The response to the signal and the impact of the corrective actions are monitored, and changes are made to the surveillance activities or REMS components as needed.

The governance of the Exalgo Alliance follows Covidien's established risk management policies and procedures. I have already touched on the risk management oversight committee. In addition, we have a well-defined escalation procedure to the executive committee of the company. As Chief Medical Officer, I chair the risk management oversight committee and I sit on the executive committee.

In summary, the Exalgo Alliance is a comprehensive program to ensure that the benefits of Exalgo outweigh the risks. It's a controlled access program, and it is designed to ensure that only appropriate patients receive Exalgo. We have defined responses to potential program deviations. Continuous monitoring and improvement is in place that gives the alliance flexibility to adapt to changes.

Our execution of the Exalgo Alliance will

reflect Covidien's commitment to good stewardship. We will be vigilant in our efforts to ensure that Exalgo remains safe and effective when used in the indicated patient population.

Thank you very much. Dr. Wright will now return to the podium for some concluding remarks.

DR. WRIGHT: On behalf of Neuromed and Covidien, I'd like to thank you once again for the opportunity to present our application for Exalgo.

In conclusion, as you've heard from Dr. Webster today, Exalgo represents an important addition to the armamentarium for opioid-tolerant patients with moderate to severe chronic pain whose current therapies do not provide adequate relief. Exalgo, administered once a day, is safe and effective for this intended patient population.

Post-marketing data confirm the safety profile established in the clinical program. Covidien is committed to the implementation of the Exalgo Alliance to assure responsible distribution, prescribing, dispensing and use of Exalgo in the intended patient population.

Finally, Neuromed and Covidien believe that the Exalgo data together with the Exalgo Alliance program support the proposed indication.

Thank you for your attention. I'd now like to address your questions.

DR. KIRSCH: I'd like to thank the sponsor for their clear presentations. I would like to remind the members of the Committee that we're now open for questions, but please don't ask your question until you are recognized by myself. With that, I open the floor to questions. I guess I'll start.

I have a number of questions related to slides CP-2, CP-3 and CP-4, and they all relate to the variance in your measurements. Those slides represented, I believe, nine or 12, some number of patients, but without any recognition of standard deviation or standard errors.

I'm wondering if you could tell me about the variance of those measurements.

DR. WRIGHT: Certainly. If we could have the -- I'll show you that in just a minute. What I can say, though, is throughout our program, what we've

noticed is that there's a very consistent picture for the variability in the pharmacokinetics of Exalgo, and what you see here are the error bars that are on this curve.

So the variability in the parameters, such as area under the curve and Cmax, are in the neighborhood of about 20 or 30 percent, which is pretty consistent across the entire program.

DR. KIRSCH: Dr. Covington?

DR. COVINGTON: Thank you. In your REMS program, you indicated that you would be monitoring for signs suggesting illegal activity. I wasn't sure what you had in mind. Do you plan to monitor electronic prescription monitoring programs, for example? Do you plan to look for multi-sourcing in your own database or in the state-run electronic databases?

DR. WRIGHT: I'd like to ask Dr. Neuman to address that question for you.

DR. NEUMAN: So your question was around what defines a potential illegal activity, or was it more around the type of databases we might be

utilizing?

DR. COVINGTON: It was both. What will you be monitoring to look for illegal activity, and specifically, will you be monitoring the state-run prescription monitoring programs?

DR. NEUMAN: We have not predefined what illegal activity represents. We recognize, however, that when you have a system that links the prescriber and the patient and the pharmacist in the way that we foresee the Exalgo Alliance doing so, that behaviors may come up, and we simply wanted to reinforce the fact that if information is developed that suggest illegal activities, we would forward that on. So it's not a preset kind of definition.

DR. KIRSCH: Dr. Vaida?

DR. VAIDA: in the labeling, in the packaging, it was hard to read here, is there actually -- do you have actual strengths of what tolerance is, like how many -- what strength of morphine a patient should be on before you should be using Exalgo?

DR. WRIGHT: Yes. There is a conversion

chart in the label. However, it is a guide to be used as opposed to very specific different -- or specific differences in terms of --

DR. VAIDA: But in that black box warning, are there minimums? What I'm going for is what we learned with fentanyl transdermal is that the real reason for a lot of errors and overdosing was the understanding of the equipotent doses. So there is actual, like you should be on three months of morphine at 60 milligrams.

DR. WRIGHT: Yes. Yes, certainly.

DR. VAIDA: Okay. I couldn't read that.

DR. KIRSCH: Dr. Morrato?

DR. MORRATO: Thank you. My questions have to do with the REMS and the implementation, and I have a few. With the Palladone, there was limited rollout with evaluation metrics. Is that planned here? I've heard that it might be targeted, but is it explicitly a limited rollout, and are there metrics in place that you've defined and the frequency of their measurement?

DR. WRIGHT: I'm going to ask Dr. Neuman to address that question regarding implementation.

DR. NEUMAN: Regarding a limited launch, if you look at non-abuse and diversion safety data, we feel that the 17 million patient days in Europe with the OROS hydromorphone represents kind of a preliminary exposure to the, again, non-opiate diversion type, but the more common adverse events.

Regarding the risk in the United States, what we're targeting is a very, very small percentage of DEA registrants. It's a very, very small percentage of current prescribers of other long-acting opioids. So that's our target market for the prescribers in the United States, and that's how we're kind of approaching getting this product to market.

DR. MORRATO: Then I just had a couple other -- clarification, then. Have you established explicit criteria for how you're going to define deviations as opposed to just in general, which was what was presented?

DR. NEUMAN: There are certain deviations that we have established around -- or certain definitions of deviations we've established around, such as if patients are presenting from a prescriber

and the prescriber is not enrolled, that would obviously be something that needs clarified.

Specifically, for the patient, we have refills that come before the expected due date, because we do track days of therapy dispensed. We also track refills that come subsequent to the expected refill date, targeting specifically whether the patient is still opioid-tolerant or not.

There are other ones. We've identified things like fatal and overdose, use for post-operative pain or acute pain or those kinds of things. So we have a series of metrics, if you will, of things that we're tracking that could represent deviations.

DR. MORRATO: Thank you.

DR. KIRSCH: I have a follow-up to that line of questioning related to slide CP-13. You talked about an appeals process. Could you be a little bit more specific about this appeals process, what the process is and what criteria will be used?

DR. NEUMAN: Yes. We understand that there could very well be behavior that's flagged as a deviation from the guidelines, which is either a

clerical error or some other reason. So at the second deviation, the prescriber or the stakeholder will be de-enrolled, will be contacted by our group within Medical Affairs, and we'll have the opportunity to request re-enrollment, and a chance to help us understand the circumstances around that second infraction.

Then it will be Covidien's Medical Affairs function's role to evaluate that and make a decision regarding reeducation and re-enrollment.

DR. KIRSCH: Will there be public members on that appeal board?

DR. NEUMAN: Currently, there is no plan for public members to do that.

DR. KIRSCH: Dr. Zito?

DR. ZITO: Thank you. I have a few questions. One, I'm wondering about incentives for prescribers and pharmacists to enroll in the program.

DR. WRIGHT: I will ask Dr. Neuman to return to address that question.

DR. NEUMAN: The incentive is serving the patients who require medication for their chronic

pain, need long-acting opioids for their chronic pain. There are no financial or commercial incentives being offered.

DR. ZITO: The second point is a question that relates to the knowledge you have on Jurnista's use in Europe in terms of market share for opiates over there.

DR. WRIGHT: I'd like to ask Dr. Richarz to come to the podium, please, to address that.

DR. RICHARZ: Dr. Ute Richarz, Johnson & Johnson. I'm sorry, I cannot give you absolute numbers on market share. Jurnista was introduced in several markets, starting with Germany, in 2006. The other markets followed a bit later.

Overall, the European markets are characterized by a variability of available products, of sustained release opiates. So the overall market share of Jurnista is still relatively small.

DR. ZITO: Thank you. And I had one final question for the moment that relates to physician specialties, because I'm not really clear what this DEA identification process would mean. DEA tracks, as

you know, physicians who are miserable prescribers or inappropriate prescribers just as much as appropriate prescribers.

So I don't quite gather how you would identify physicians who would be likely to be the most appropriate prescribers for this drug.

DR. WRIGHT: So the most appropriate prescribers would be those with experience with long-acting opioids. But I would like to ask Dr. Neuman to give you a little bit more detail.

DR. NEUMAN: For our commercialization efforts, we have targeted physicians who -- if you're familiar with the definitions about who falls within deciles five through ten of prescribers; that is, they are the more frequent opioid prescribers.

But we've taken it further and we've limited that population to those prescribers who have a history of prescribing multiple long-acting opioids. So if you're in that decile five through ten, but you only prescribe a single long-acting opioid, you would not be eligible for our commercialization activities.

Also, if your practice is mostly limited to

short-acting opioids, you would not be someone we would target our commercialization activities toward. So we've taken that universe and we've shrunk it down to those people who have experience using multiple long-acting opioids currently, and that works out to be -- if you accept the number of a million DEA registrants, and that's just a number that's commonly used, I assume it's relatively accurate, it represents on the order of 1.5 percent or less of DEA registrants, and it's a similar small, single-digit percent of current OxyContin prescribers is who the group is that we're targeting our marketing efforts.

DR. ZITO: So if I interpret that correctly, then this would mean that any and all physician specialties are represented in the pool.

DR. NEUMAN: That is correct. We are not screening for specialty training, in part because of the relatively small number of pain management trained practitioners relative to the population as a whole. The last number I saw was approximately 6,000 pain management facilities in the United States to serve the entire 50 states. So we're not putting a screen

around what type of residency, say, they complete.

DR. KIRSCH: Dr. Lesar?

DR. LESAR: My question has to do with hospitals, hospitalized patients, patients who might be admitted on Exalgo, patients who might want to be started, and how the pharmacies would be required to be enrolled both for their inpatient and outpatient and how would that be operationalized?

DR. NEUMAN: Your question is regarding enrollment of pharmacies within hospitals.

DR. LESAR: Correct, and how would they verify patients, who would be expected to do that, how would you track drug use? Hospital pharmacies may dispense to inpatients, as well as outpatients. So, obviously, large amounts of long-acting opiates are used in hospitals.

DR. WRIGHT: Thanks for that clarification.

Dr. Neuman?

DR. NEUMAN: Hospital pharmacies will be part or may be part of the Exalgo Alliance. They will go through the same types of procedures. We will, however, be able to sequester those hospitals within

the database that -- the hospital pharmacies within the database. So that we're trying to minimize the flags, because you could legitimately get a prescription filled at a community pharmacy on Monday, be hospitalized on a Wednesday, and that would normal flag as an early refill. So we have to work around that.

But except for that kind of sequestration, the rest of the rules and the policies and procedures of the alliance would apply whether the patient is in the inpatient setting or the outpatient setting.

DR. LESAR: Just to follow-up. So it would require that the admitting physician, which is unlikely to be the enrolled physician, to enroll in the program; is that correct?

DR. NEUMAN: It's impossible to tell. It is, actually, in my experience, in my practice experience, more common that you find pain management support in the inpatient setting. So a patient who is acutely hospitalized may actually have better access to a pain specialist who would likely be in the Exalgo Alliance.

But you're right, there could very well be situations where the physician, the attending physician or perhaps an anesthesiologist on staff would have to be enrolled in the alliance to continue this process.

DR. KIRSCH: Dr. Lorenz?

DR. LORENZ: Thank you. I have a few questions about the Study 301. My first question is how many patients were screened in order to enroll the 459 participants, and what were the major reasons for exclusion.

DR. WRIGHT: I'll ask Dr. Gallen to address that question.

DR. GALLEN: 808 patients were screened. One of the biggest factors is that you needed to have the 60 milligrams per day exposure to morphine, because we wanted to focus this on the opiate-tolerant patients who seemed to be our major targets. That was probably the largest thing.

In addition, there were certain concomitant medications and medical conditions that were excluded conditions, but conceptually, the most important one

was the amount of medication they had been on.

DR. LORENZ: It's striking to me that 340 out of 459 patients did not complete the study. I wonder if there were differences between those who did not complete and those who did, including their baseline pain scores or pain co-morbidities.

DR. GALLEN: In terms of the specific question, the patients in general who came into the study had moderately severe pain. Their baseline pain score between those who did not complete and those who did complete was very similar to each other. That really wasn't the distinguishing factor.

The distinguishing factor had much more to do with a tolerance for the medication and whether they got pain relief from the medication, which I think really refers back to a lot of the sort of biological factors.

So that patients who were inappropriately treated, when they came in and were adapted to, for example, 75 percent of their initial dose -- so patients may have come in, they were poor responders, they were put on 75 percent of that poor responder

dose. A number of patients dropped out at that point, because they had been put on a lower level of opioids. That was sort of your first wave of discontinuations.

In the course of the titration, an additional number of patients came in who either had adverse events with hydromorphone or who had other additional -- who had other problems with it, in some cases, opiate withdrawal; in some cases, administrative issues.

DR. LORENZ: Yes. But I'm confused by your statement, because you said that there was no difference in baseline pain scores, but then you explained the dropout rate by saying that those who dropped out were those who were inadequately treated with the change in pain medication, that their baseline control was probably ineffective.

So how could there have been no difference, and yet those who dropped out were those who were ineffectively managed?

DR. GALLEN: In other words -- sorry I wasn't clear -- patients who came into the trial, by definition, had inadequate control of their pain,

because they had moderate to severe pain, and in general, that level of inadequate control at the time that they came in was very similar across the patients who continued and the patients who dropped out.

What differed between the two was their response to the medication over the course of titration. So in other words, the patients who, in the first few days or the first week, when they were put at a lower dose of medication, didn't get relief, significant number of dropouts.

The patients who didn't get essentially about the 3.2-point drop in pain over the course of the trial, significant number of dropouts. So the patients who you get at the end of the titration period are the patients who are hydromorphone responders.

DR. LORENZ: So just to summarize, 40 percent of the patients dropped out during the change from their baseline opioid to the Exalgo, and I think what you're saying is that those patients were essentially non-responders to Exalgo.

Now, the other question that I have, given

that 70 percent of the patients dropped out, is to ask you how you understand the change in scores over the course of the trial. A one-point change in a pain intensity score and a two-point change, these are different scores between the intervention and control group, how do you understand those as minimally clinically significant differences?

My understanding is that some investigators would actually require higher different scores to claim a clinically important difference.

DR. GALLEN: That's a great question. In terms of considering the significance of the pain score, I think that, obviously, the first point that we had made was that in terms of the special protocol assessment defined protocol, we met the original criteria.

But from there, you then look at the pain score, which was about 1.1-point difference. There are several different ways that you can consider that.

The first thing to understand about the pain scores is the fact that the difference between the baseline and the final result depends a lot on the

details of the trial design. So, for example, if one looks at the OPANA ER trial, where you were comparing against a pure placebo, so you have a larger contrast, you get about a 2.2-point change.

If you looked at one of our comparator trials, where we compared about half-strength Exalgo, you got a 0.7-point change. This trial, where you're comparing against Placebo plus rescue medication, where the rescue medication was about a fifth of the dose of the Exalgo, you got about a 1.1-point change. So the question is is that 1.1-point change meaningful.

One way to think about that that's commonly used for the opiates is to look at the percent of the population who had a 30 percent reduction in their pain or a 50 percent reduction, where we saw significant differences at the 30 and 50 percent reduction levels between Exalgo versus placebo.

Another way you can think about it is how does the patient see this. How does the patient identify that 1.1 change in their symptoms? And there, the patient global assessment is really quite

helpful. So, for example, if you look at the data, you can see that placebo dominates the poor and fair response categories, while Exalgo dominates the good, very good and excellent categories, which, of course, is what we're targeting is good, very good, excellent. Those are the people who we we think get a benefit.

A third thing you can say is does this matter in the real world, does this have any effect on people's lives at all. And that's where you would look at things like the Roland-Morris Disability Questionnaire, getting the impact of this on disease.

When you look at this data, there are a couple of things that are interesting. The first is that you have separation of drug from placebo, and I might note, from prior clinical trial experience, getting a separation between drug and placebo on a disability measure in a three-month trial is no mean feat. That's a significant thing.

The second thing, you can see that they've separated by about week eight, continuing. And the third, you can see the trend of the lines as the placebo continues to worsen and as the treatment

continues to get better.

So from our point of view, the signal that we get is within the ballpark of what one would expect for pain trials with the specific features of this design. The patients themselves saw it as good, very good or excellent, and it actually made a real difference in terms of changing people's lives.

So we consider this to be a clinically meaningful event.

DR. LORENZ: Sure. I guess my only other comment would be that you're missing outcomes on 340 of the original cases. And so, obviously, there's no way to account for that if it wasn't measured.

DR. GALLEN: And I think that that's a really important point, that not everyone will respond to the medication. I think this goes back to the data that Dr. Webster showed, which shows that when you take a general population of pain patients and you put them on a given opioid, something like 30 to 40 percent will respond to the first opioid. When you then moved them to the second opioid, an additional 30 percent will respond, and it takes several drugs to

get the right one.

This design basically selects for the patients who are able to respond to the drug, which is, of course, what would happen in clinical practice. Thank you.

DR. KIRSCH: We are going to go on for another five minutes of questions, which means that we'll cut our break time to 10 minutes from 15 minutes. Dr. Denisco?

DR. DENISCO: Thank you. I would like to know if the risk management plan that has been instituted in Europe is anything similar, or if there's any comparison to the alliance that has been rolled out somewhere else that it can be compared with.

Then paired with that is the -- you mentioned a group of physicians. Are they going to be targeted or only allowed to be this certain group, and how does this affect the regulation of the practice of medicine, which is a state function, from a legal standpoint? That's one question, and I have one other.

DR. WRIGHT: To address your question regarding the REMS that we have compared to the risk MAP that's being used in Europe, certainly, there are differences and I'll ask Dr. Karen Naim to describe the risk MAP in Europe.

DR. NAIM: Good morning. I'm Dr. Karen Naim from Johnson & Johnson, and I can describe the E.U. risk management plan for Jurnista. The E.U. risk management plan does consist of both a pharmacovigilance plan and a risk MAP, or a risk Minimization Action Plan.

The pharmacovigilance plan in the E.U. risk management plan includes routine surveillance activities, which involve inter-product signaling of the company's safety database, which is called Scepter, to monitor for adverse event reporting trends, as well as lot trend review to detect potential manufacturing issues.

It also includes data mining of the WHO VigiBase database, which is the health authority database for use in Europe. The pharmacovigilance plan also includes product-specific surveillance

activities, which again makes use of the company's safety database, but includes periodic monitoring of trends and a demographic profile of cases reporting adverse events of interest, which include misuse, abuse, diversion, overdose, as well as some others.

In terms of the risk minimization action plan, it's primarily education and monitoring, where we monitor for supply chain integrity, for manufacturing product quality complaints, as well as some specific launch activities and an educational program, which is implemented in the countries in which the product is launched.

DR. KIRSCH: Please use your microphone.

DR. DENISCO: This alliance program has not been used elsewhere then.

DR. WRIGHT: Components of it have been used. We've taken components from other risk management plans to use in this, but this specific plan, no, has not been used.

DR. DENISCO: The reason I ask that, because in slide CS-12, it was just briefly mentioned if there was this high level of education of physicians and

patients and pharmacists, that there were three cases of medical personnel splitting the tablets, and that's a fairly low hanging fruit sort of problem to encounter.

For medical personnel splitting a controlled release or time release tablet seems like a fairly large error. So I was curious if they were educated in the same way you propose to educate in the United States.

DR. WRIGHT: We have used a lot of data to develop our REMS, that being some of the data to design it. I'll ask Dr. Herb Neuman if he would come back to the podium to tell you how we're addressing that.

DR. NEUMAN: The clinical trial did not have the type of professional education or training around the things we're seeing in the REMS. So those behaviors, as Dr. Wright just alluded to, some of those behaviors actually drove some of the educational initiatives that we've taken so far, and in fact, we've gone on to validate that that message is actually being received by those folks who reviewed

the information.

DR. KIRSCH: We have seven additional people who want to ask questions and we're not going to have time to do that before the break. We'll keep this list and in the next question session, we'll start at the beginning of this new list.

We'll now take a short 10-minute break. Committee members, please remember that there should be no discussion of the meeting topic during the break amongst yourselves or with any member of the audience. We will resume in 10 minutes, which is 22 minutes after 10.

(Whereupon, a recess is taken.)

DR. KIRSCH: All right. It's 10:22 on my clock, and I'd like to welcome the presenters for the FDA portion of this meeting, and Dr. Kilgore will start off the presentations.

DR. KILGORE: I'm just waiting for my slides. Thank you.

Good morning. My name is Elizabeth Kilgore, and I'm a medical officer in the Division of Anesthesia, Analgesia and Rheumatology Products. This

morning, I will be presenting the clinical efficacy and safety review of Exalgo.

We have a little glitch. Okay. Thank you. This presentation will include discussion of hydromorphone immediate release and extended release, Exalgo regulatory history and clinical development, then efficacy and safety findings. Specific safety issues unique to this product will also be discussed, followed by concluding remarks.

Much of my presentation has already been covered. Therefore, I will be able to move rather quickly through the first few slides.

Hydromorphone is a semisynthetic hydrogenated ketone of morphine. Like morphine, it acts on the mu opioid receptors. It was first synthesized in Germany in 1921, and has been used clinically as an analgesic in the United States since 1926.

We've already heard that Dilaudid was the first FDA-approved immediate release hydromorphone. The injectable formulation was approved in 1984, and later, oral solution and tablets were approved for the

indication of management of pain, both acute and chronic, where an opioid analgesic is appropriate. Dilaudid is a Schedule II drug. Schedule II drugs have the highest potential for abuse and risk of producing respiratory depression.

Dilaudid is a potent analgesic, as can be seen on the Dilaudid label, which provides an opioid analgesic potency table which compares Dilaudid potency to other opioids. On this table, you can see that Dilaudid at 6.5 to 7.5 milligrams is equivalent to morphine at 40 to 60 milligrams; thus, Dilaudid is approximately five to eight times more potent than morphine.

We've already heard that Palladone was the first FDA-approved hydromorphone extended release for the indication, as noted, and we've already heard about the regulatory history. So I'll move forward.

The Advisory Committee recommendations for Palladone's risk management included the following -- a phased rollout, with the goals to promote appropriate and safe use, reduce abuse and minimize diversion; a surveillance system designed to collect

and analyze data in a timely manner with the use of pre-specified outcome measures and interventions; and an education component to allow for a mechanism to educate physicians regarding the risk of opioids, in general, and Palladone, in particular.

Palladone's final FDA-approved risk management program did incorporate the recommended and required risk strategies, as previously discussed. These included appropriate labeling, which consisted of a package insert and medication guide; education for the health care provider, patient and caregiver with professional labeling; a surveillance system for regular monitoring to allow for identification and intervention as problems were identified through surveillance outcomes; and a limited promotional rollout. The limited rollout will be discussed in more detail, to briefly describe the model which was developed by Purdue.

The product was to be rolled out over an 18-month period. Promotional detailing by sales representatives was to be focused on single entity opioid prescribers. In the first six months,

marketing was limited to those prescribers most likely to treat patients requiring Palladone use in the specialty areas, as noted. After that, other prescribers would be added.

There would be limited and targeted sales force for the first six months, then additional sales force pending the review of market research. Metrics surveillance outcomes were to have been evaluated at months six, 12 and 18.

As we've heard, as part of Purdue's abuse liability assessment, they conducted an in vitro dissolution in alcohol study, which showed that a high percentage of hydromorphone dose was dumped into 10 milliliters of 40 percent ethanol after 15 minutes.

To follow up that study, they performed an in vivo alcohol interaction study. This was an open label, four-arm PK crossover study to evaluate the effect of the co-ingestion of Palladone 12 milligram capsule with eight ounces of 40, 20 or 4 percent alcohol or water.

The results of the in vivo study showed that the average peak hydromorphone concentration was up to

six times greater with 40 percent alcohol than with water. The integrity of the extended release formulation of Palladone was defeated, resulting in a significant potential for dose dumping. As a result of this safety concern, Pursue agreed to voluntarily suspend sales and marketing of Palladone in the United States in July 2005.

Exalgo is the current product under consideration for approval as a hydromorphone extended release drug for the uses, dosage and indication as previously stated.

The key regulatory history has already been discussed, and therefore, I will move forward to discuss efficacy. The key efficacy study designed has been well-outlined. This table shows the analysis of the primary endpoint, the change from baseline to week 12 or final visit in the pain intensity numeric rating scale scores between drug-treated and placebo-treated patients. The baseline pain score is the score obtained after the subject had been titrated to an effective dose of Exalgo.

Therefore, a smaller change from this

baseline to the end depicts continued efficacy for the treatment given. A larger change in the positive direction indicates higher pain scores for the treatment given.

As shown in this table, the mean change from baseline for Exalgo was lower than that for placebo, 0.6 for Exalgo compared to 1.7 for placebo. This was shown to be statistically significant, with a P value less than 0.001.

This figure illustrates the proportion of responders for each treatment arm, with the range of possible levels of improvement to define response. The X-axis represents percent improvement in pain from screening and the Y-axis is the proportion of responders. For example, you can see that 37 percent of subjects who were randomized to Exalgo had a decrease of at last 30 percent, compared to 22 percent of the placebo at 30 percent.

Overall, the graph shows that the Exalgo arm has a higher percentage of responders than the placebo arm over the range of response levels up to 70 percent. It should be noted that responders were

calculated based on the change from screening baseline to the end of the study, and patients dropping out were considered non-responders.

At this time, I will discuss safety. The report of this data is preliminary, as the review is ongoing. There were 3,075 patients in the pooled safety analysis for chronic pain, with 420 exposed to study drug greater than six months, and 141 greater than 12 months. The daily doses ranged from 6 milligrams to almost 2 grams.

I will next discuss deaths, serious adverse events, common adverse events, and adverse events which led to discontinuation. Deaths -- there were no deaths in the Phase 1 clinical trials or in the key efficacy study. As can be seen, there were a total of 64 deaths in all treated patients, two in controlled studies and 62 in uncontrolled studies. There were no deaths in the placebo arms of the controlled studies.

Both of the deaths in the control trials occurred after study drug was discontinued, with study drug appearing unrelated to causality. No deaths appeared definitely or probably related to study drug.

No trends could be identified regarding diagnosis, dosage or time on study drug as to causality.

It was noted that the majority of deaths occurred in cancer patients and appeared related to disease progression. I have provided selective narratives for the two subjects in the two control studies whose death causality appears unrelated to Exalgo.

Subject one was a 68-year-old male with metastatic squamous cell lung cancer. He was on multiple concomitant medications and had many co-morbidities. He died four days after study drug was discontinued. The cause of death was respiratory failure. In this patient, with underlying lung cancer, it would appear that causality is unrelated to study drug.

The second subject was a 70-year-old male with metastatic cancer, who also was on multiple medications and had extensive co-morbidities. Death occurred 19 days after study drug was discontinued, and appears unrelated to study drug.

Serious adverse events -- there were a total

of 240 patients who experienced at least one serious adverse event in the Exalgo-treated patients compared to placebo, where there were eight out of 466 who experienced at least one SAE.

As can be seen, gastrointestinal disorders was the most frequently occurring system for serious adverse events in the Exalgo-treated group. The most common GI events were vomiting, nausea and constipation. Infections and infestations were second highest and included pneumonia, 11 Exalgo versus one placebo, and cellulitis, seven in Exalgo versus zero in placebo.

General disorders and administration site conditions were next highest. This category includes chest pain, 12 in Exalgo, zero in placebo; drug withdrawal syndrome, five in Exalgo versus one in placebo; and disease progression, seven in Exalgo versus zero in placebo.

Serious adverse events were noted to be dose-related, increasing in frequency with increased dosage. Note that the proportion of SAEs in the Exalgo-treated is higher than those in placebo. This

difference may in part be due to the fact that the placebo control studies were conducted in non-cancer patients.

Common adverse events -- this table summarizes the most common adverse events that occurred in greater than or equal to two percent of patients in the controlled and uncontrolled studies, expressed in approximate percentages. As can be seen, the most common AEs were GI-related constipation and nausea, as may be seen in opioids, followed by vomiting, then central nervous system AE of somnolence.

Adverse events leading to discontinuation -- this table represents adverse events which led to study discontinuation, as reported in greater than or equal to one percent of patients with chronic pain in controlled and uncontrolled studies. GI-related AEs were the most common reason for discontinuation, followed by somnolence.

There are three specific safety issues related to this product, which include OROS technology, alcohol interaction, and abuse and misuse.

As has been covered, the OROS tablet is covered with a non-digestible, semipermeable membrane, with a single laser-drilled orifice on the drug side to allow the exit of the drug. Once the drug is out, the emptied outer shell is excreted unchanged.

The combination of an opioid with the known risk for constipation with a semi-indigestible drug product raised concern that there may be an increased incidence of gastrointestinal-related adverse events in this product.

There have been literature reports of the formation of Medicare bezoars with associated GI obstruction in some OROS products. A bezoar is defined as a mass or concrete formation of partly or wholly undigested material found in the GI tract.

In addition to GI obstruction, bezoars have also been associated with other GI complications, to include ulceration, hemorrhage, gastritis and perforation.

This table summarizes the number and types of possible OROS formulation-associated GI events reported in Exalgo-treated patients. There were six

reports of GI obstructive events, two reports of small bowel obstruction, and one report each of gastric outlet obstruction, intestinal obstruction, fecaloma, and bezoar. The contents of the bezoar were not confirmed on endoscopy, so it could not be determined that it was undigested OROS shell.

There were four reported cases of GI perforation events, one each perforated sigmoid colon, large intestine, bowel, and diverticulitis with perforated sigmoid colon. Other serious adverse GI events not specifically falling into either of these categories, but determined to be treatment-related GI SAEs, included the following -- one GI disorder characterized by severe nausea and vomiting; three additional cases of severe nausea and vomiting; three reported cases of constipation resulting in an SAE; one diverticulitis without perforation; and one report of upper abdominal pain.

Overall, the following trends were observed in the GI events. All GI obstructive events occurred in the uncontrolled studies. All patients who experienced a GI obstructive event had significant

pre-existing GI history, such as prior abdominal surgeries, and in one case, Crohn's disease. Most of the patients presented with nonspecific complaints of nausea, vomiting and constipation.

Exalgo interaction study. The Exalgo interaction in vitro and in vivo data show that the extended release profile of Exalgo is maintained in alcohol and there is no significant dose dumping effect.

Dr. Gong of the controlled substance staff will discuss the abuse liability study later this morning.

In conclusion, Exalgo OROS hydromorphone extended release appears efficacious in the population studied. It has a similar adverse event profile to other high potency opioids. It does not dose dump in alcohol, and may have similar risks in terms of GI obstruction and bezoar formation as other marketed OROS formulations. This concludes my presentation. Thank you.

Dr. Greene is next.

DR. GREENE: Thank you.

Good morning. My name is Patty Greene, and I'm a drug use analyst in the Division of Epidemiology, Office of Surveillance and Epidemiology. Today, I will be presenting the outpatient drug utilization trends for hydromorphone products.

The outline of my presentation will be in the following order. First, I will present a cell distribution analysis for hydromorphone products. Next, I will present dispensed prescription and patient data for years 2006 to 2008. I will begin by comparing hydromorphone utilization trends to selected opioid pain products.

The top five prescribing specialists for year 2008 will be described for products included in the selected market. I will also discuss diagnosis codes associated with the use of hydromorphone products, and then finally, I will conclude with a summary of my presentation.

The following hydromorphone products were included in the analysis -- immediate release hydromorphone tablets and oral liquid, including marketed brand and generic products, from years 2006

to 2008. Injectable hydromorphone products were not included in this review.

The selected opioid pain products included in the analysis are presented on this slide. Chemical groups include oxycodone, methadone, morphine, fentanyl, oxycodone, and extended release formulations. The selected opioid pain products were broken into immediate and extended release formulations.

Products include brand and generic oral formulations. All products are grouped by chemical name and divided into immediate or extended release formulations. The immediate release dosage forms include oral solid and liquid products, and extended release dosage forms included long-acting tablets or capsules and the transdermal patch formulation. All combination oral products are grouped by chemical name. For example, oxycodone and acetaminophen products are grouped under the chemical name oxycodone.

This analysis includes only Schedule II controlled substances. Hydrocodone, codeine and all

injectable formulations were not included in the analysis.

So let's start with cell distribution data for hydromorphone products. We used the IMS Health IMS National Sales Perspective database to get a sense of where these products were distributed, and to determine the primary setting of use.

This database measures the volume of products and units amd dollars, moving from the manufacturer to retail and nonretail channels of distribution. Sales volume is measured by eaches. Eaches represents the number of bottles or packets in each shipping unit. Products are shipped to retail or nonretail channels.

The retail channels include chain, independent, mass merchandisers, food store pharmacies and mail order pharmacies. Nonretail channels included federal facilities, nonfederal hospitals, clinics, long-term care facilities, home health, HMO and miscellaneous channels, including prisons and university.

So when we examine the wholesale data for

year 2008, it indicates that the majority of sales for hydromorphone were distributed to retail pharmacy settings, 67 percent. Thus, the remainder of my analysis includes outpatient utilization patterns, excluding mail order channels.

Next, we will analyze prescription data. We examined prescription data using SDI, or Surveillance Data, Incorporated. This database provides a national level projected prescription and patient-centric tracking service. It receives over two billion prescription claims per year, and represents over 160 million unique patients.

The number of dispensed prescriptions is obtained from a sample of 59,000 pharmacies throughout the U.S., which account for nearly all retail pharmacies in the country, and represent nearly half of all retail prescriptions dispensed nationwide.

The types of pharmacies included in the retail sample are national retail chains, mass merchandisers, data from pharmacy benefit managers and physician provider groups.

This graph displays total dispensed

prescriptions for all selected products by chemical group from year 1999 to year 2008. For the selected opioid products included in the analysis, hydromorphone ranks fifth overall. Hydromorphone would be about here at the very bottom. This market includes both immediate and extended release formulations.

When total dispensed prescriptions are grouped by product form, immediate versus extended release, total dispensed prescriptions for both immediate and extended release products increased from a combined total of approximately 53 million prescriptions in year 2006 to nearly 65 million prescriptions by year 2008.

Immediate release products accounted for 47 million prescriptions, or 72 percent of the selected market in year 2008. For the same period, extended release products accounted for 18 million dispensed prescriptions, or 28 percent of the market.

This graph compares hydromorphone to other immediate release products. Overall, hydromorphone ranked third among the selected potent immediate

release oral opioid pain products, and has a slightly higher market share than immediate release morphine products by year 2008. Extended release products accounted for a combined total of 18 million prescriptions by year 2008. The top three extended release products included oxycodone, fentanyl and morphine.

This graph displays the total number of projected patients and expensed prescriptions for hydromorphone products dispensed from retail pharmacies. Total dispensed prescriptions for immediate release hydromorphone products increased by 34 percent between year 2006 and 2008. For the entire review period, approximately 4.8 million prescriptions were dispensed to 1.7 million patients. For year 2008, hydromorphone accounted for nearly 1.9 dispensed prescriptions and over 760,000 patients.

We also examined the top five prescribers of immediate release opioid products in year 2008. The top five prescribers included general practice, family medicine and doctors of osteopathy, internal medicine, anesthesiology, orthopedic surgery, and emergency

medicine.

The leading prescribers were general practice, family medicine and doctor of osteopathy specialists, with approximately 9.5 million prescriptions, or 20 percent of the market. Internal medicine was 6.4 million prescriptions, or 14 percent of the market, followed by anesthesiology and orthopedic surgery, with seven percent of the market, respectively.

For extended release products, the top three leading prescribers were similar to immediate release products, followed by physical medicine and rehab with nine percent, and nurse practitioners with five percent. For hydromorphone, again, the top three prescribing specialists were similar to both immediate and extended release products. Emergency medicine prescribers ranked fourth and accounted for roughly 110,000 prescriptions, or six percent of hydromorphone prescriptions in year 2008.

Finally, we will examine diagnosis data using office-based physician surveys. To determine the top diagnosis codes associated with the use of

hydromorphone in year 2008, ICD-9 codes were grouped by disease and injury categories. Diseases of the musculoskeletal system and connective tissue groups -- and that would be here -- were the top diagnosis category, with 27 percent of response by survey, followed by the injury category, fractures, sprains, contusions and injuries, as well as follow-up examinations, with 15 percent each.

In summary, for years 2006 to 2008, approximately 4.9 million hydromorphone prescriptions were dispensed to 1.7 million patients in the outpatient retail pharmacy setting. Total dispensed prescriptions for hydromorphone products increased 34 percent between years 2006 and 2008. However, these products accounted for only one percent of the selected opioid market share in 2008.

The top five prescribing specialists for hydromorphone included general practice, family medicine and doctors of osteopathy specialists, internal medicine, anesthesiology, emergency medicine, and physical medicine and rehab.

Lastly, the top three grouped ICD-9

diagnosis codes associated with the use of hydromorphone included musculoskeletal system; fractures, sprains, contusions and injuries; and, followed by follow-up examinations.

Thank you. Next, we'll have Cathy Dormitzer.

DR. DORMITZER: Good morning. My name is Cathy Dormitzer, and I'm an epidemiologist in the Division of Epidemiology in the Office of Surveillance and Epidemiology. Today, I'm going to provide a brief background on the Drug Abuse Warning Network, otherwise known as DAWN. I'm going to present some initial findings, the methods used to calculate estimates on drug abuse ratios, the estimates themselves, and the summary and conclusions drawn from these estimates.

The Drug Abuse Warning Network is a public health surveillance system that's administered by SAMHSA, which is the Substance Abuse and Mental Health Services Administration. Data are collected based on nationally representative multi-stage probability sample of hospitals that have emergency rooms, and

detailed information on drug-related emergency room visits are collected, and that allows them to provide national estimates of these visits.

For this analysis, national estimates for a variety of comparator drugs were requested from SAMHSA. The criteria for selection was similarly scheduled opioid analgesics, normally Schedule II, like hydromorphone. And when there was immediate release and extended release formulations, separate estimates were requested for each release type.

But not all comparator opioid analgesics were included in this analysis. If the relative standard error is greater than 50, the estimates are suppressed, because there's too much imprecision in the estimate. The national estimates produced for oxymorphone and for fentanyl transdermal products -- excuse me -- transmucosal products resulted in RSEs that were greater than 50, and so those estimates were suppressed and we could not include them.

Estimates for morphine products included ED visits that tested positive for morphine in the toxicology screen. And since heroin and other opiates

will result in a positive morphine test, these drugs weren't included as a comparator because there was a possibility of too many false positives.

Hydromorphone is a Schedule III drug, and only in immediate release formulation, but it was included because of the large number of prescriptions and because it's been included in so many other analyses

Here are the national estimates of all drug-related emergency room visits by drug type, and this is from year 2004 to 2007. The estimates for 2008 are to be released shortly, but not in time for this Advisory Committee.

As you can see, the national estimates for the ED visits related to hydromorphone is considerably lower than for the comparator drugs. There were approximately 6,000 ED visits related to hydromorphone in 2004, and that rose to approximately 18,000 ED visits related to hydromorphone in 2007.

For all formulations of oxycodone, both immediate and extended release, there were close to 81,000 ED visits in 2004, and 160,000 visits in 2007,

and similar estimates were found for hydrocodone. There were also about 80,000 in 2004 and about 153,000 ED visits in 2007.

The fentanyl estimates could only be provided for transdermal products, which is an extended release product. And in 2004, there were close to 16,000 ED visits and -- wait a minute. There were 15,000 in 2004 and 30,000 in 2007.

Now I'm showing the estimates by release type, and the estimates are the same for hydromorphone, 6,000 in 2004 and 16,000 in 2007, and that's the same for the hydrocodone products. But for oxycodone, this is just the numbers for immediate release product, and what you can see is there are about 38,000 ED visits in 2004 and about 75,000 in 2007.

Even though hydromorphone is an immediate release product, I just put it here so that you could compare it to the extended release products for oxycodone and then transdermal, because it was a fentanyl transdermal, is considered an extended release. It's also on this slide. What you can see

is that for oxycodone extended release, in 2004, there were about 48,000 visits, and in 2007, it was about 90,000 visits. And for fentanyl transdermal, about 15,000 in 2004 and about 30,000 in 2007.

Now, for this analysis, we examined two data elements that were collected in DAWN. There was case type, which includes cases that are not related to misuse and abuse, such as suicide attempt, adverse reaction, accidental ingestion. But I will be focusing on drug misuse and abuse.

Another data element was case disposition, which provides information on the seriousness of the ED visit, because it is generally assumed that patients that were discharged home were not as serious as the ones that were either admitted to the ICU or other hospital department.

Now, SAMHSA has constructed two case definitions to understand better drug misuse and abuse. First, there's cases related to the nonmedical use of pharmaceuticals, and that's otherwise known as NMUP, and these were ED visits that were either classified as over-medication, in other words,

exceeded the prescribed dose, seeking detox, or the case type "other," which was generally used to classify drug abuse cases.

Then there's cases related to all misuse and abuse, also called ALLMA, and these are ED visits that include all the NMUP cases, but it includes ED visits where there were illegal drugs or alcohol present. So ALLMA is a little bit more expansive than NMUP.

The proportion of cases that were either related to NMUP, nonmedical use of pharmaceuticals, and ALLMA, all medical misuse and abuse, these are just simple percentages. All four years of data from 2004 to 2007 were summed to provide one estimate, because the proportions did not vary that much by year. So this makes it simpler to present.

As you can see, the proportion related to NMUP, or nonmedical use of pharmaceuticals, as well as ALLMA, all misuse and abuse, was somewhat lower for hydrocodone, an immediate release product, and for the immediate release formulations of oxycodone than they were for fentanyl transdermal and for the extended release oxycodone. The proportion for hydromorphone,

the immediate release product, it was in between immediate release and extended release formulations.

To provide information on the seriousness of ED visits, SAMHSA also developed two constructs based on case disposition; required follow-up, therefore, the ED visit has a more serious outcome and does result in either being admitted to that same hospital or transferred to another hospital institution; and did not require follow-up, and that would be the cases that were either discharged home or left against medical advice.

Again, all four years of data, 2004 to 2007, were summarized into one estimate, and as you can see, the proportion that required follow-up was somewhat lower for oxycodone -- excuse me -- for hydromorphone and for the immediate release oxycodone products than for fentanyl and the extended release oxycodone. Again, hydromorphone fell into between these two groups.

Now, we did see in a previous presentation by Dr. Greene that the number of retail prescriptions for hydromorphone is considerably lower than for all

other comparator drugs and is closest to fentanyl, but still, fentanyl has roughly three to four times more retail prescriptions than for hydromorphone. And that's important that these differences in drug utilization be kept in context when examining drug-related health outcomes, and that's why drug abuse ratios were used.

DAWN can provide estimates on the nonmedical use of opiates, but it does not include information on drug exposure or availability or drug utilization data. So drug utilization data is used as a proxy for exposure and availability. So DAWN is used as a numerator, and drug utilization from VONA is used as the denominator.

This slide is a summary of the number of ED visits associated with the nonmedical use of pharmaceuticals per 10,000 retail prescriptions. As you can see, the NMUP ratios for hydromorphone, currently marketed as an immediate release product, are higher than the ratios for immediate release oxycodone and for hydrocodone, and is somewhat lower than the extended release formulations.

This was also found for the ALLMA ratios, which is all misuse and abuse. The ALLMA ratios for hydromorphone, again, are higher than the ratios for the immediate release formulations and lower than the extended release formulations.

When examining these ratios, it's very important to keep in mind certain limitations. These data, DAWN and VONA, are in no way linked. There is no information provided by DAWN on how many patients had prescriptions, or if a member of their family had a prescriptions, and that's an important limitation.

The sampling methodologies that were used to derive these national estimates are in no way linked, and as a result, confidence intervals of these ratios cannot be derived. The populations are similar because they are both national estimates, but DAWN is the population of emergency rooms/hospitals and VONA is a population of retail pharmacies.

Lastly, when estimates are small, it's generally expected that the confidence intervals are going to be larger, because they produce less-precise estimates. So it's difficult to compare estimates

based on -- or ratios that are based on small estimates to ratios that are based on very large estimates.

At the same time, the ratios, as well as the proportions of NMUP and ALLMA, are consistent, and in absolute numbers, the public health burden of hydromorphone appears to be lower, but the number of ED visits are increasing as drug utilization increases.

The drug abuse ratios related to hydromorphone products are higher than for other immediate release opioids and somewhat lower than the extended release products. Thank you.

Now, it's Dr. JianPing Gong.

DR. GONG: Good morning, everyone. I'm JianPing Gong from the controlled substance staff. The purpose of my talk is to describe the abuse liability of Exalgo.

Since Exalgo is a new formulation of hydromorphone, I will talk about the abuse potential of hydromorphone first. The abuse potential of a substance is an essential factor in determining the

schedule for the substance and the CSA. There are five schedules under CSA. These schedules are designated as Schedule I, II, III, IV and V.

Drugs in Schedule I and Schedule II have the highest abuse potential, whereas drugs in Schedule V have the lowest abuse potential. Schedule I substances do not have approved medical use. Drugs in Schedule II, III, IV and V have approved medical use. Hydromorphone has a high potential for abuse, and as such, is a Schedule II opioid.

From the scientific point of view, hydromorphone is a highly abusable drug. Here, I want to present a recent paper that describes the abuse potential profile of three opioids. In 2008, Walsh et al published the paper in "Drug and Alcohol Dependence" to compare the abuse potential of hydromorphone with hydrocodone and oxycodone.

There is now the subjects -- how opioid abuse in volunteers. The administration load is low.

I have listed all of the dosages used in the study. Walsh et al, merges subjective effects, observed rated effects, and physiological effects. I

copied the figure here for the measurement of "how high are you." What you can see here is the curves of hydrocodone and oxycodone are very close to each other. The hydromorphone response seems to be a little bit greater than for hydrocodone and oxycodone. The authors concluded that hydromorphone was most definitely more potent, less than two-thirds, than either hydrocodone or oxycodone.

Now, I will move to describe the abuse potential of Exalgo, which represents a new formulation of hydromorphone. The Federal Food, Drug and Cosmetic Act requires the assessment of the abuse potential of a product under review by the agency.

The abuse potential of a product impacts the safety of the product. Information related to abuse potential is included in the labeling, and is weighted in the risk-benefit assessment of the product.

Clinical data used by CSS to assess abuse potential are derived from pharmacological studies, the abuse-related AE profiles in clinical trials, and the human abuse potential status. For my assessment, I will present data from two clinical studies.

The first trial I will describe is an abuse potential study, Study 22. Our focus is subjective effects. The second trial is the efficacy study, Study 301, where we focus on drug accountability.

Study 22 is an abuse potential study. The study subjects are opiate-experienced, non-dependent volunteers. The study included three phases -- the screening phase, Phase A and Phase B. The screening phase determined that the subjects, that we are able to distinguish the control, hydromorphone, from the placebo, which was a requirement for entry into the controlled clinical trial, Phase A.

Phase A included five arms -- placebo control, placebo, and three different dosages of Exalgo. The 8 milligram dosage of Exalgo was manipulated by the sponsor to overcome the extended release properties, and the sponsor referred to this as the altered dosage.

Only the subjects who tolerated the high dose of Exalgo were allowed in Phase B. Phase B consisted of two groups -- placebo control, 8 milligram immediate release hydromorphone, and Exalgo,

64 milligrams, the highest dosage.

This figure shows the PK data of the study. The X-axis is different time points, plus dosing in hours. The Y-axis is the concentration of hydromorphone in plasma in nanogram per milliliter. Basically, two groups of peaks are seen in this figure. The first group of peaks is high and narrow. The pink, immediate release hydromorphone, and the green, altered Exalgo, curves overlap, indicating that PK profile of altered Exalgo is very similar to immediate release hydromorphone.

The second group of peaks is delayed and wide reflects the extended release of hydromorphone. These curves also indicate that different dosages of Exalgo are proportional.

This figure shows the time course of drug liking. The X-axis is different time points plus dosing. The Y-axis is the drug liking VAS. VAS is a visual analog scale. It is used to quantify some measures, in this case, drug liking. The scale is from zero to 100. Zero means strong disliking; 100 means strong liking.

The subjects used a mouse to move the small vertical bar to answer the question, "At this moment, my liking for this drug is." In this figure, you can also see two groups of peaks. The first group of peaks is high and narrow. The pink, immediate release hydromorphone, and the green, altered Exalgo, curves are very close to each other.

So the PD profile of altered Exalgo 8 milligram is very similar to hydromorphone immediate release 8 milligram. The second group of peaks is delayed and wide. It included three different dosages of Exalgo. So as shown by these two figures, the PK/PD profiles correlate well.

I want to point out that no data points were collected between hour 15 and hour 24 post-dosing, and the importance of this is that we don't know if higher subjective effects measurements could have been seen during this period.

These four figures show the time course of good effects VAS, high VAS, opium organista (?) scale, and take drug again VAS. All these four figures have the similar pattern as the previous one showing two

groups of peaks. What I want to highlight here, again, is the profile of Exalgo. These peaks are broad, high and sustained for many hours.

Subjects reported a high measure of good effects, feeling high, opium organista subjective effects, and want to take the drug again for at least 20 hours.

The second clinical trial, Study 301, was a drug efficacy study. My FDA colleague, Dr. Kilgore, has already discussed this trial. What I'm going to do is, from the CSS point of view, to evaluate drug accountability in this study.

Drug accountability can be considered a surrogate measure for potential drug abuse and diversion. The sponsor selected and provided narratives of 85 patients with drug accountability problems. They referred to them as patients of interest.

Of 85 patients, one subject was suspected of diversion, but this was not verified. So our evaluation is based on 84 patients. We are addressing two questions here. First, what percentage of

patients had drug accountability issues? Secondly, how much drug are we talking about? This is the percentage of tablets that were not accounted for.

In this clinical trial, only two groups of patients received Exalgo, one during the titration phase, the other during the double-blind phase Exalgo group. 459 subjects started at the titration phase. Of these, 268 completed and 191 discontinued treatment. Of those patients discontinuing during titration, 54 showed drug accountability problems.

During the double-blind study, 134 subjects started and 66 completed the study. Six of them had problems; 68 discontinued; 24 of them had a problem. Overall, 26 percent of patients had drug accountability issues.

Now, we will evaluate how much drug was missing using the tablet count as our measure. The number of dispensed minus the number of taken is the number of tablets that should be returned. The number of should be returned minus the number of actually returned is the number of missing.

The number of missing divided by the number

of tablets that should be returned times 100 percent is the percentage of missing. Finally, we have figured out that overall, 36 percent of tablets were missing, which is contributed by both completing patients and discontinued patients.

Discontinued patients include two subgroups -- patients who discontinued at the titration phase and the patients who discontinued at the double-blind phase. In conclusion, more than one-third of the drug tablets that should have been returned were not accounted for.

Based on the data presented, our conclusions are hydromorphone has a high abuse potential comparable to oxycodone. The PK/PD profile of altered Exalgo 8 milligrams is similar to that of hydromorphone immediate release 8 milligram. Exalgo has a high abuse potential, as indicated by the intensity and the duration of the positive subjective effects. There is a high level of drug unaccountability during the clinical efficacy study.

Taking all this information together, we predict that Exalgo will have high levels of abuse and

diversion. Thank you.

Dr. Perla will give the next presentation.

DR. PERLA: Good morning. I'm Jeanne Perla, and I work with the Division of Risk Management in the Office of Surveillance and Epidemiology. This morning, I will provide an overview of the risk management activities at the FDA, to further guide the discussion about the specific risk management for Exalgo.

My presentation will include an overview of the history of the Food and Drug Administration Amendment Act, and the elements of the risk evaluation and mitigation strategy, or REMS. FDA has conducted several public and stakeholder meetings as a result of asking manufacturers of opioids to work together to create a single shared REMS. I will review the progress of these efforts, followed by the differences in the components of two recently approved opioids, Onsolis and Embeda. In conclusion, I will summarize this information.

Title 9 of the Food and Drug Administration Amendment Act, or FDAAA, gives the FDA new authority

to require post-marketing studies and clinical trials, requires sponsors to make safety-related labeling changes, and requires sponsors to develop and comply with REMS. Subtitle (a) took effect March 25th, 2008.

What is a REMS? A REMS is a required risk management plan that uses tools, as specified in FDAAA, that goes beyond routine professional labeling, necessary to ensure that the benefits of a drug outweigh the risks. A REMS is enforceable and is included with the approval letter.

A REMS may include one or more of the following elements -- a medication guide or patient package insert is approved FDA patient labeling that helps a patient understand the risks of a drug. The communication plan is the FDA-approved materials to aid sponsors implementing REMS, and to inform health care providers about serious risks.

Some REMS may also include elements to assure safe use, which may include one or more of the following -- prescriber training or certification; certification of dispensers; drug administration restricted to certain health care settings;

documentation of safe use prior to dispensing; monitoring patients; and enrollment of patients in a registry.

When considering which elements to assure safe use to be included in a REMS, it is important to remember that a REMS must be commensurate with specific serious risks listed in the labeling, not be unduly burdensome on patient access to the drug, and as much as possible, conform with elements of other drugs with similar serious risks and be designed for compatibility with established distribution, procurement and dispensing systems for drugs.

When managing opioid risks, the agency's concerns include the increased abuse, misuse, addiction and accidental overdose associated with long-acting and extended release opioids. Previous voluntary risk management programs have been ineffective in addressing these risks. Most programs involve voluntary education to health care providers and patients.

In early 2009, the agency notified affected opioid sponsors that a REMS would be required for

certain opioids to ensure that the benefits of the drug would continue to outweigh the risks. The FDA then held five additional opioid REMS meetings to allow affected sponsors, stakeholders and other interested persons and organizations the opportunity to present comments and information on the elements of a REMS program, how to minimize the burden of multiple REMS programs on the health care community and patients, while ensuring the benefits outweigh the risks, and how the FDA should assess the effectiveness of the REMS.

As the agency considered the development of opioid REMS, we realized multiple opioid REMS programs have the potential to cause a burden to the health care system, making it difficult for the prescribers and other health care providers to be fully aware of each program, which in turn could limit patient access to appropriate opioid pain medication.

Because multiple opioid products have similar risks, manufacturers of long-acting and extended release opioid formulations were urged to develop a single shared REMS so as not to overwhelm

the health care system. In response to this request, manufacturers formed an industry working group to work together to achieve the goals of maintaining access, while reducing abuse, misuse, addiction, and accidental overdose.

So where are we now? We have met with the manufacturers, concluded the public and stakeholder meetings in May, and the call for comments period has ended. The manufacturers, stakeholders, public meetings have been transcribed, and we received over 2,500 comments to the docket.

The FDA has formed a steering committee to review all transcripts from the meetings and comments submitted, including those from the industry workgroup. The agency is currently considering the next steps. At this time, there is no approved single shared REMS system.

I'm now going to describe the REMS of the two opioids the FDA has approved, to give you an example of the range of REMS programs. On July 19, 2009, the FDA approved Onsolis. Onsolis is a transmucosal fentanyl product for the treatment of

breakthrough pain in cancer patients who are also receiving and tolerant to opioid therapy.

Onsolis has a more restrictive plan due to additional risks compared to immediate and extended release opioids. Therefore, it will not be included in the single shared opioid REMS. One major risk is the potential for medication errors. Fentanyl products are not bioequivalent. However, there are reports of prescribers and pharmacists substituting one fentanyl product for another. Another risk is improper patient selection, such as prescribing fentanyl products to opioid-naive patients.

The approved REMS program for Onsolis is called the Focus program. It is a restricted program that includes a medication guide, a communication plan and elements to assure safe use. The elements to assure safe use require educating and enrolling the health care provider, specialty pharmacist, and patient.

The implementation system for the Onsolis program includes special certification and enrollment of distributors, maintaining a database of all

enrolled health care providers, patients, specialty pharmacists and distributors; monitoring the distribution of Onsolis; monitoring the dispensing of Onsolis by specialty pharmacists via certified carriers to the patient's home; monitoring, auditing, evaluating all active pharmacies and distributors to ensure Onsolis is distributed where and when it needs to be.

The implementation system monitors and evaluates the REMS program, working to improve the implementation of the elements, to assure safe use and modify elements that are not effective. Finally, the assessments will be submitted every six months for a year, then annually thereafter.

Embeda was approved August 13th, 2009. It is an extended release opioid used to manage moderate to severe pain when a continuous around-the-clock opioid analgesic is needed for extended periods of time. Embeda's risks are similar to other long-acting opioids. Once the shared single opioid REMS is approved, Embeda will be among the other opioids to implement the new REMS.

Embeda was approved with an interim REMS that consists of a medication guide and a communication plan. This is similar to the current risk management programs of the other approved extended release opioids.

In summary, the FDA has new authority to help address serious risks. The final single shared, long-acting extended release opioids REMS are still being developed. It is important to remember that risk management should reduce identified risks, while minimizing health care burdens and barriers to access.

Two opioids with different risks have been approved, one with a restrictive REMS program, the other with an interim risk management program. Exalgo REMS should conform with the elements for other drugs with similar risks.

Thank you.

DR. KIRSCH: I'd like to thank the FDA presenters for their excellent presentations. We'll now go on to the next question-and-answer session. I'd remind the members of the Committee to please don't speak until you're called on. Please use your

microphone. For this question-and-answer session, we'll be able to ask further questions of the sponsor, as well as the FDA.

So we'll go back to our list that we had before the break, and Dr. Markman is next.

DR. MARKMAN: John Markman. This is a question for the sponsors. The Exalgo Alliance program, the centerpiece seems to be stakeholder education and the PPMA, outlined in CR-24.

As a clinician who prescribes opioid medication, I would like to understand a little bit more about how this PPMA would handle a negative urine drug screen on a patient taking this medication.

What would be the next steps? How would that be enforced? And I think most importantly, how would that signal be detected, as was discussed in CC-18? So a negative drug screen, how would the signal be detected, and what would the clinician be expected to do with the patient, per the PPMA?

DR. WRIGHT: Dr. Neuman, please.

DR. NEUMAN: The education for the physician and the material that's included as part of the PPMA

does address positive urine drug screens. The exact response of the individual clinician to an individual patient who has that is really the practice of medicine, and that's up to the clinician to use whatever techniques or policies that they have developed in their practice how to deal with that specifically.

We will have information available to the clinicians talking about urine drug screens, talking about how to use them, if that would be helpful to the clinician. But that individual patient with an individual drug screen is really part of the doctor-patient relationship.

DR. MARKMAN: So could you just put that in the context of the studies where 33 percent of the medication was not accounted for? Again, is there any way that that signal feeds back to make this REMS more robust? That's, I guess, my question.

DR. NEUMAN: Well, the percentage you're quoting is from the clinical trials that didn't have the elements to assure safe use as part of the clinical trial, that wasn't in there. So I'm not sure

you can make an apples-to-apples comparison on that.

The signal of a positive urine drug screen would not be rolled up, if you will, to the Exalgo Alliance unless the practitioner chose to report that. Again, that individual patient relationship is with the clinician.

DR. MARKMAN: Is there a mechanism for reporting that in the European model, or what would be the mechanism to report that and who would they report it to?

DR. WRIGHT: So we'll have to ask Dr. Karen Naim to report that, based upon her experience with the European risk MAP. I do want to point out that, as I'm sure you have noticed, there are many differences between the REMS that we are proposing for the U.S. and the risk MAP that's available in Europe.

DR. NAIM: Dr. Karen Naim, Johnson & Johnson. As Dr. Neuman stated, that would be a spontaneous report that the physician could make to the company in the same way it would happen in the United States.

DR. MARKMAN: And the company would do what

with that information? Where would that go from there?

DR. NAIM: All of the spontaneous adverse event reports are summarized both in routine surveillance, so in the context of the periodic safety update reports for the product, as well as in the reporting that's done specifically for the risk management plan.

So in addition to periodic safety update reports, we also summarize data elicited from the data streams, from the risk management plan, and report those to the agency.

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: I've got three questions. First, I'm concerned about -- not concerned, but I have a question about the packaging, because you had mentioned in the presentation that there are patients that walk around with several hundred pills, and with children, in particular, even a handful of pills is of significant concern. The smallest dose that I saw that's proposed right now is an 8 milligram dose and higher not dose, but pills.

So putting all that together, what is the effect, or have you studied the effect of multiple pills swallowed at a single time? I'm looking at the single dose pharmacokinetics and you get the peak levels with the various doses.

A child may swallow four, five, six, ten pills at one time. There may also be a situation where those pills are crushed. I didn't know if any studies had been done or reports have been received from Europe about multiple pill ingestions.

DR. WRIGHT: I think, if I understand your question, you're interested in the pharmacokinetic profile or the bioavailability of multiple tablets.

DR. DESHPANDE: That's correct.

DR. WRIGHT: And the answer to that question would be based upon the data we have -- of course, I didn't show that -- but in some of our pharmacokinetic studies, multiple tablets would result in the bioavailability -- based on linear pharmacokinetics of Exalgo, of essentially giving the bioavailability for that dose that was given.

So, for instance, two of the 4 milligram

tablets would behave like an 8 milligram dose.

DR. DESHPANDE: Of an intact pill.

DR. WRIGHT: Correct.

DR. DESHPANDE: The second question I have is about the direct marketing. I had heard in the presentations that the company does not plan to do direct marketing to consumers at this point. Is this a binding situation if the drug is approved by the FDA?

DR. WRIGHT: I don't believe that's binding, but it is a commitment that has been made, yes.

DR. DESHPANDE: If I may ask one last question. This may be for you or the FDA. But in the FDA presentations, we were reminded that the REMS plan is an enforceable plan. Is that enforceable -- it comes back to your question -- enforceable to the -- again, the physicians, the pharmacists or the company? Who is held responsible in this process?

DR. WRIGHT: So if I can try and clarify your question.

DR. DESHPANDE: For me, a REMS is, I heard the term, an enforceable plan. And when

enforceability comes in, there's an accountability. Who is the accountable party, I guess?

As was asked by Dr. Markman, where does this go if there is a variation from the REMS that's detected?

DR. WRIGHT: So from our perspective, let me ask Dr. Herb Neuman to address that question.

DR. HERTZ: Let me, also, while Dr. Neuman is taking that long walk again, describe that our authority in enforcing the REMS is with the company. We don't have any direct authority for any of the interactions with physicians or patients.

DR. NEUMAN: That was going to be my answer. The responsibility rests with the NDA holder.

DR. KIRSCH: Another question, Dr. Deshpande?

DR. DESHPANDE: I don't want to belabor the point, but I think abuse potential is one of the things that we're discussing here, and part of -- this is a very nicely described REMS program. From what I heard, it's internal to the company, and therefore, one of the questions, again, that it comes back to is

how is a person -- what do you do with that information, because if this is a voluntary agreement between the pharmacy and the company, the physician and the company, not a contractual agreement, then it becomes -- there is a different level of enforceability or accountability that comes in.

So how do you see this working, actually?

DR. WRIGHT: I'll ask Dr. Neuman to return, please.

DR. NEUMAN: You raise a couple of very good points. We recognize, and actually, based on advice from some experts in the field we've been working with, that we would benefit from having an external expert group serve as an information resource and additional oversight.

So we're in the process of developing that. I didn't put it in my presentation, but we are committing to have that in placed prior to the launch of Exalgo, because we agree that having an external set of eyes could be very, very helpful in making sure that we're not missing anything internally, but, also, we're conforming to what's going on in the field in

the practice of pain management.

DR. KIRSCH: Dr. Hertz?

DR. HERTZ: When the REMS is in place, there need to be assessments made periodically, and when information is presented to us, if we see that there are substantial deviations, our authority can come into play, again, in terms of working with the company to have those problems addressed.

This is all still new territory for us, but it is a requirement that there be assessments. We'll also be following the available databases.

DR. KIRSCH: I'd like to have one follow-up question to Dr. Deshpande's first question, which is the pharmacology of having two tablets, each with their own little individual laser hole, versus one tablet with one hole.

The response to this question was that a 16 milligram tablet would respond in the same way as two 8 milligram tablets if they are swallowed. That doesn't make any sense to me pharmacologically if one of the key elements of your tablet is the single laser hole. Could you expand on that explanation, please?

DR. WRIGHT: Certainly. I guess maybe I could say if you doubled the dose, you would see double the concentrations of hydromorphone, and that would be based upon the fact of linear pharmacokinetics for hydromorphone.

But if you were giving two different tablets, the response that you would have, the pharmacokinetic response would be that total dose that you're administering.

DR. KIRSCH: But in one paradigm, there is a single table tablet with a single hole. In the other paradigm, there's two tablets with two holes, and you say they're identical.

DR. WRIGHT: I'm sorry. I didn't mean to suggest that there were any tablets with two holes. Every tablet has one laser-drilled hole. Am I misunderstanding your question?

DR. KIRSCH: Dr. Deshpande's question, at least as I understood it, was if you have a child -- and Dr. Deshpande is a pediatric intensivist -- who has ingested five 8 milligram tablets, is that the same -- will that have the same impact as the

administration of a single, if it was available, 40 milligram tablet?

DR. WRIGHT: That's correct, it would.

DR. KIRSCH: Okay. The next question is by Ms. Solonche.

DS. SOLONCHE: Thank you. Now that Jurnista is being used in other countries, what kind of data are you seeing on levels of misuse, abuse and diversion?

DR. WRIGHT: So I'll ask Dr. Karen Naim if she would come to the podium to explain that.

DR. NAIM: Karen Naim, Johnson & Johnson. So abuse and intentional misuse are, again, monitored in surveillance of the spontaneous cases reported to the company, and as I mentioned in my previous response, covered in the standard section of the periodic safety update report.

We do look at a broad range of events in the PSUR review, which include possible abuse/misuse cases, including cases of withdrawal, which are reviewed for evidence of abuse. Again, these are trended and as part of -- the spontaneous reports are

trended by quarter as part of the pharmacovigilance plan activities for the E.U. RMP.

During the period from 2006 through the end of 2008, there have been no cases reporting the specific preferred terms "drug abuse" in the database. There are two cases that reported intentional misuse, and I have those summarized here on the slide.

The first was a patient who took 16 milligrams instead of the prescribed 8 milligrams. There were no further details provided in this case, other than that -- I'm sorry -- with regard to why or the intent of taking that 16 milligrams as opposed to 8. The patient experienced sleepiness, tiredness and hypertension, which did subsequently resolve.

The second case reporting intentional misuse is a patient who was prescribed 16 milligrams per day and was reported to have, acting on her own authority, increased the dose to 48 milligrams per day to treat a sudden increase in pain, and that patient was hospitalized for an accidental overdose, from which she recovered two to three days later.

There was, also, with regard to the

withdrawal syndromes cases, there was one case describing withdrawal syndrome that, upon review, did report a drug-seeking behavior, but no further information.

DS. SOLONCHE: Thank you.

DR. KIRSCH: Dr. Yesenko?

DR. YESENKO: This question is for the sponsor. Actually, specifically, REMS, you've mentioned that you're having now an oversight committee, and I believe Dr. Neuman mentioned that you would have outside experts. Is that the case or not?

DR. WRIGHT: I'll ask Dr. Neuman to answer that question.

DR. NEUMAN: Yes. Our plan is to bring together a group of external experts in the area to meet periodically, both to review the work that our own risk management oversight committee has done, but as I said earlier, also, keep us attuned to what is going on in the practice of pain medicine.

DR. YESENKO: Thank you. Then the market share question was not answered about Jurnista for Europe. Will the market share information be

available for Exalgo, as well, or how will that be handled?

DR. WRIGHT: The market share data will be available to Covidien.

DR. NEUMAN: As part of both the periodic reporting to the Food and Drug Administration, as well as our reporting around the REMS, market share data will be included as it is available to us.

DR. YESENKO: So was it made available for Jurnista or not?

DR. NEUMAN: Let me clarify. I was referring to the U.S. sales of Exalgo. I don't know how market share data is gathered in Europe. But our intent is to share market share data in the United States as part of our regular filings with the agency.

DR. YESENKO: And then do you plan to market the 64 milligram at all?

DR. NEUMAN: We have no intention of marketing the 64 milligram tablet.

DR. YESENKO: Was Jurnista marketed under 64 milligram in Europe?

DR. NEUMAN: My understanding is, yes, it is

currently marketed as a 64 milligram tablet, in addition to other sizes; but currently, yes.

DR. YESENKO: Thank you.

DR. KIRSCH: Dr. Zito?

DR. ZITO: I'm trying to get a fix on the post-marketing surveillance goals and activities, and I sense that there is something of a separation here, that this is focused on diversion and misuse and whatever all those terms that refer to inappropriate use.

But is there no part of it that really deals with the safety dimension in appropriately used cases? That's one question. My second question, it seemed to me, and this might be the FDA person's question, the Onsolis plan, it sounded to me from the bullets like maybe there's a drug registry involved there, and maybe that gives us a good deal more information about both effectiveness and safety, which would be very nice to understand, if that's the case.

DR. WRIGHT: Could I have the slide that has the pharmacovigilance? Let's talk about the pharmacovigilance for a second. In a moment, I'll put

up a slide that I used in my presentation.

There's really three pieces of safety assessment. We did spend a lot of time on the Exalgo Alliance implementation database, and that's really what you're hearing about. But Covidien maintains pharmacovigilance activities, we do currently and we always have.

So routine drug safety surveillance, all the things that go into pharmacovigilance will be happening with Exalgo, just as they do with our other products. The difference here is we'll be having new data input for Exalgo from the implementation database that we don't have with any of our other currently marketed products.

DR. ZITO: And a follow-up to that point, then. If physicians are not required to report and if all we're going to get is spontaneous reports, which are horribly under-reported, then where are we in terms of an improved safety surveillance system as a result of having all this activity around the REMS?

DR. WRIGHT: In our education materials, in the enrollment for the physician and for the patient,

and I believe for the pharmacy as well, we do talk about reporting of adverse events. We have both a committee and operated 24-hour call center for the intake of adverse event reports, but we also have a call center specific to the Exalgo Alliance.

So there are venues for gathering this information, and certainly, we will gather the information. We also have specific ways of following up for certain key signal events that we're particularly interested in. But there is no contractual stimulation or some drive that we can go to force reporting.

DR. ZITO: And I guess the other point I had raised was about whether we're really looking at a drug registry. For example, we have past experience, like clozapine, for example, very close monitoring of everybody who got the medication. I don't sense that that's -- would that be possible here?

DR. WRIGHT: That is currently not our plan for the Exalgo Alliance, to have a formal registry type. We do collect information on prescribers and patients and pharmacy as far as the drug and the dose

and other things.

But when we sat down to design this system, we wanted a comprehensive system, but we recognized the need to balance the safety with the access and with burdening the health care system, and we felt that we could achieve our safety goals without turning it into a more-formal registry type of a study.

DR. KIRSCH: Dr. Flick?

DR. FLICK: A couple of questions for the sponsor. With regard to the REMS, can you tell me, who is it actually that enrolls prescribers? Is it your regular sales force that's charged with enrolling prescribers, and if so, what's their incentive and do they have -- is their sale incentivized? Then is reporting incentivized for your sales force?

DR. WRIGHT: The sales force is not going to be a driver of enrollment. We intend to use medical science liaisons as a primary source of enrollment. We also expect most -- we expect some physicians or prescribers will self-enroll via the Exalgoalliance.com Website. So there are multiple ways for individual prescribers to enroll.

I believe you also asked me a question about the incentive of, I think, the sales force it was, if that's right. The sales force compensation, if you will, involves many objectives, and some of those objectives are around reinforcing safety messages during their interactions with prescribers.

I don't know if enrolling, per se, is part of their objectives, but I believe the sales force is well-aware that is only through the safe and effective use of Exalgo that the product will be commercially successful.

So they are tasked with supporting REMS and they are compensated, if you will, as far as how they support the REMS activities.

DR. FLICK: So I would ask, is there any specific incentive for your sales force, who will be the primary contact people with the prescriber? Is there any incentive for them to report inappropriate prescribing?

DR. WRIGHT: It is company policy that they report that. There is not a financial incentive, per se. It is expected of them. We do spend a lot of

time -- I spend a lot of time working on the training of the sales force to make sure that they understand their responsibilities, and also, the corporation's responsibilities towards these behaviors and capturing them.

We do have a fairly good rate of adverse event reporting coming through from the sales force into the corporate office, and I would fully expect similar compliance around many kind of behaviors with the prescribing of Exalgo.

DR. FLICK: A second question, if I might. One thing that concerns me, and it reflects some of Dr. Deshpande's comments, the use of -- a child or potentially an adult may suck on these tablets.

Is there pharmacokinetic data that looks at blood levels when these are placed in the mouth?

DR. WRIGHT: No. We have not done any studies holding the tablet in the mouth and looking at the pharmacokinetics.

DR. FLICK: Just a few minutes ago, I just Googled Concerta and found a very nice description from a young man who describes how to suck on Concerta

tablets to defeat the shell. I think that's concerning. And I wonder, have you considered using something noxious under that shell, like capsaicin?

DR. WRIGHT: No. We have not given any consideration of that for this product at this point in time.

DR. FLICK: I think that has been investigated, hasn't it?

DR. WRIGHT: I am not aware of that.

DR. KIRSCH: Did you have another question, Dr. Flick?

DR. FLICK: If I might.

DR. KIRSCH: Yes, sure.

DR. FLICK: For the FDA, who controls the base drug source, the hydromorphone source for the manufacturer? Does the FDA control that?

DR. WRIGHT: Dr. Rappaport?

DR. RAPPAPORT: Are you asking about the drug substance they use to make the product?

DR. FLICK: Yes.

DR. RAPPAPORT: In terms of control --

DR. FLICK: Is there an allocation?

DR. RAPPAPORT: -- oversight -- sorry.

DR. FLICK: Is there an allocation for a company?

DR. RAPPAPORT: Yes. There is some control over that through the DEA, although our controlled substance staff is very involved with that as well.

DR. FLICK: Does FDA have the opportunity to restrict, through the DEA, the allotment that they receive should they not live up to the expectations of the REMS?

DR. RAPPAPORT: Our controlled substance staff expert says no.

DR. FLICK: Thank you.

DR. KIRSCH: Dr. Covington?

DR. COVINGTON: This is, I guess, mostly clarification. As I understand the REMS, there's a surveillance part, but the rest of it pretty much seems to be predicated on ensuring that the prescriber and the patient are well-educated. And I'm wondering, do we have data to tell us to what extent knowledge deficit actually accounts for the problems that we have with prescription drug abuse and diversion,

number one.

Number two, if I understood your graph earlier, you indicated that 80 percent of the prescription drug abuse and diversion or abuse was illegitimately obtained.

So I'm assuming that all this education program we have would essentially only address 20 percent of the people who might be abusing the substance. Am I on track with both of those?

DR. WRIGHT: I'd like to ask Dr. Stemhagen to address that question.

DR. STEMHAGEN: To address your question about the elements of the REMS and then education, there is education, certainly, and that comes first, but then the key points are attestation and enrollment.

So a prescriber must read the enrollment form, which is an attestation to follow safe use procedures, to confirm that they understand exactly how to use the product and so on, and that's signed.

Then there's also the PPMA, as I described, and that is for the prescriber and the patient to have

the dialogue and the education, but then they must both sign that, as well.

So with that, it's that the patient is acknowledging they understand. There's a part in there that says "I've had the opportunity to speak with my physician, all my questions have been answered."

So it's not only the education, but assuring that they have understood what they need to do, and that should stimulate the dialogue, and it is signed by both of them. So it's a lot more, actually, than education alone.

DR. KIRSCH: Dr. Lorenz?

DR. LORENZ: I have two questions and a comment. The first question, I wondered, most abuse seems to occur through the diversion of prescriptions that are given for legitimate medical ends or through medications obtained through a physician.

I wondered, in your experience with the drug in Europe, is the drug that comes into supply, does it result from first prescriptions that go unused, maybe because they're not effective, or is it non-adherence

to the drug as prescribed over the course of use? Do you have any sense of what proportion under the latter condition would be sort of free drug?

DR. WRIGHT: I'll ask Dr. Richarz to address that question, please.

DR. RICHARZ: There is indeed not such detailed information about that. Abuse of prescription opiates is, in relation to abuse of other drugs, much lower in Europe. Therefore, most of the surveillance systems do not explicitly focus on that. So I'm afraid I cannot give you a clear answer on that.

DR. LORENZ: It's information that one could obtain through surveillance, though, no doubt. Here's my comment, and that is that the approach to REMS that we're talking about here, I don't mean to demean it entirely, but it does strike me as an approach to preventing shoplifting through posters that say "please behave well," and penalizing checkout clerks and store managers.

So my question is, if the real issue seems to be drug that goes unused that's left in supply,

whether pricing approaches would be more effective ways to incentivize patients, who are actually the ones who possess the drug once it's dispensed.

In particular, I wonder whether the manufacturer has considered issues like if most drug, excess drug in supply results from, for example, inappropriate targeting of initial prescriptions, especially since see through the data here that only 30 percent of patients even completed a clinical trial, then maybe in certain populations, initial prescriptions should be higher cost, so that physicians and patients make better decisions about their initial use of such a drug; or, if there's non-adherence of some proportion of drug and we can estimate that proportion, whether we could develop a pricing policy that, for example, would increase the marginal cost of unit doses beyond some average used under normal clinical circumstances.

So I wonder what the manufacturer thinks of that and its ability to influence retail pricing as part of a REMS.

DR. WRIGHT: I'll ask Dr. Neuman to address

your question.

DR. NEUMAN: We have not looked at differential pricing or using price as a motivator to try to reduce the amount of product that may be available to be diverted, because you're right. If product is consumed as prescribed, it's not likely to be available for diversion.

But I want to back up and talk a little bit more about the educational piece. When I was in practice, I'm an internist by training, I was in a semi-rural county of Florida, and I can't tell you the number of times a patient came in, usually an older patient, with some kind of knee pain, back pain or whatever, and during the history, said, "Well, my wife gave me a couple of her pain pills."

I'm sure neither intended to break the law, and I'm sure neither one intended to harm the other, but they didn't know any better. And what I'm a little embarrassed to tell you is I didn't necessarily address it either as the prescriber.

So I think there is a knowledge gap. I think there is a way that we can responsibly educate

patients that this stuff is potent, it has value to somebody who might choose to steal it, and you could kill, which is pretty much what we say, a loved one if you allow them to take it from you.

So I think by education, we can drive a lot of these behaviors to help minimize the amount of drug that's available for diversion. As far as your pricing strategy, I was sitting there, it's a very intriguing concept, and I think it's something worth talking about, but I believe that since 80 percent or so of the diversion comes from a source that you know, a physician or a thing, that's really where we're focused on, and I think that's where the educational pieces have the biggest effect.

DR. LORENZ: My only other comment would be that it does seem that take-back would be a really important thing to consider, and that it would be valuable for the agency to work on allowing take-back, because that is another way to get an unused drug and, in fact, it would allow for novel pricing strategies beyond the one that I conceptually described that I think should be considered.

DR. WRIGHT: I'm going to let Dr. Rappaport have the final word in this area.

DR. RAPPAPORT: Thanks. While we agree that that is a really -- probably would be a very useful strategy, at the moment, it's not a legal strategy. Under the Controlled Substance Act, the only people who can take back controlled substances are policing authorities. You have to have the patient take it to their policemen, who don't want it.

There are a lot of people thinking about that, and we're having a lot of discussions with other agencies -- and there's some interest in Congress, as well.

DR. KIRSCH: The open public hearing is a very important part of our day, and so I don't want to delay that. So we're going to stop here for lunch.

For the participants of the panel, lunch will be served in the Montgomery Room for members of the Committee. We will return promptly at 1:00 from lunch. We will reconvene again in this room for the remainder of the session. Please take any personal belongings with you that you might want to have during

this time.

For the Committee members, please remember there should be no discussion of the meeting during lunch amongst yourselves, with the press or with any member of the audience.

Thank you.

(Whereupon, at 12:09 p.m., a lunch recess was taken.)

A F T E R N O O N  S E S S I O N

DR. KIRSCH: We're going to restart our meeting. Both the Food and Drug Administration, FDA, and the public believe in a transparent process for information-gathering and decision-making. To ensure such transparency at the open public hearing session of the Advisory Committee meeting, the FDA believes that it is important to understand the context of an individual's presentation.

For this reason, FDA encourages you, the open public hearing speaker, at the beginning of your written or oral statement, to advise the Committee of any financial relationship that you may have with the sponsor, its product, and if known, its direct competitors. For example, this financial information may include the sponsor's payment of your travel, lodging, or other expenses in connection with your attendance at the meeting.

Likewise, FDA encourages you, at the beginning of your statement, to advise the Committee if you do not have any such financial relationship. If you choose to not address this issue of financial

relationships at the beginning of your statement, it will not preclude you from speaking.

The FDA and this committee place great importance in the open public hearing process. The insights and comments provided can help the agency and this committee in their consideration of the issues before them.

That said, in many instances and for many topics, there will be a variety of opinions. One of our goals today is for the open public hearing to be conducted in a fair and open way, where every participant is listened to carefully and treated with dignity, courtesy and respect. Therefore, please speak only when recognized by myself, and thank you for your cooperation.

The first speaker is Patricia O'Hara. I'd ask you to go up to the microphone behind you. When you begin speaking, the green light will go on, and when your time is up, the microphone will stop, and we'll ask you to stop speaking at that point.

You may begin.

MS. O'HARA: My trip has been paid for and

my lodging has been paid for, and I'm very happy to be here. I used to fear a very painful death until I dropped dead on my kitchen floor about five years ago with a major heart attack and a blood clot in the main artery to my heart.

I was lucky that I had my son there on my couch in the next room, recovering from a fall off a roof and had broken his back and was there to give me CPR and call 9-1-1. The medics came and I had to be defibrillated four times. The cath lab took three hours to bring me back, and I think I died a couple more times in the hospital.

But I found that dying is still a lot easier than living with pain every single day, and I've lived with lots of pain over lots of years. I had a laminectomy 30 years ago due to a disk on a nerve. I've had peripheral vascular disease. I've had a hip replacement. I've ruled out osteoporosis. Luckily, I don't have that yet. And I couldn't walk probably less than half a block. I still have problems walking, especially uphill, since my new diagnosis is lumbar spinal stenosis.

I probably like more than anything to shop. I'm what you call probably a shopaholic. And what I found myself doing was having everything delivered to my front door, not only clothing and things like that, but even groceries at times.

Friends stopped inviting me to go with them to fairs, because I just couldn't keep up. I just couldn't walk far enough.

I have an HMO, and at that particular time, several years ago, they were not giving out pain medication to anyone in the HMO, much less someone who repeatedly asked for it with pain.

I happened upon the study through a radio program and was accepted into the study with Northwest Clinical Research in Bellevue, Washington, and it was wonderful. It took a short time to get up to the milligram level of my pain. I think I ended up at 16 milligrams for my pain.

But it didn't last long enough. It lasted about two weeks, and then they started tapering me down and I could tell by the second day that they were taking it away. But it's the first real relief that I

had had in a long, long time.

What I had done in the past is to self-medicate. I would go to Canada, over the border, and buy bottles of 200 Tylenol with -- acetaminophen with codeine in it, and I'd bring back about eight bottles or 1,600 pills at a time.

I would take -- well, my doctor gave me lots of Tylenol. So I had lots of Tylenol, maybe up to 24 Tylenol a day. And I finally figured that I'm not even going to have a liver here pretty soon unless I do something about it.

But since I went through the study and talked to my doctor, he has now agreed to put me on a semi-long pain medication. Right now, I'm on methadone twice a day, but I really would like Exalgo to get on the market. I'm very anxious to be able to take that again.

There will probably be more pain. There might be more surgery. But I know I can look forward to an excellent drug. Thank you.

DR. KIRSCH: Thank you. The next speaker is Denise Zamora.

MS. ZAMORA: As he said, my name is Denise Zamora. I've come all the way from northwest Washington State. I actually canceled an appointment to speak with some of our Congressmen on an issue that has overwhelmed my life since last year at this time.

I've had to hire help to take care of my husband around the clock. I've had to have someone to take -- hire someone to take my child back and forth to school twice a day and to operate my business. So other than the usual, customary courtesy of providing travel and lodging, I've incurred great expense to come here, because it was very important to me.

For the last several years, I've endured debilitating pain, and it affects every aspect of my life. It is so severe that it wakes me while I'm asleep. I've tried nearly every kind of treatment and therapy available. I have utilized the benefits of pain management specialists, and have been reduced to trying several various unsatisfactory medications just so I could function.

I will attempt to briefly describe my experience with Exalgo compared to other analgesics.

When I use the typically prescribed medications for those with similar painful afflictions, I have to anticipate each day's activity. I have to estimate how long I might be standing, sitting, driving, essentially, how difficult every task might be.

Most of the time, my schedule consists of the usual family and business activities, as well as things that come up without notice. I have to remember not to forget my medications, and try not to panic should I leave them behind.

There is always the concern about taking an extra dose due to overwhelming pain, and it is also distressful to me to have to take a prescribed dose, even when I feel that I don't need it.

Exalgo allowed me to resume all normal activities prior to my painful condition. Exalgo permitted me to refuse being defined as a victim of my own body. I regained the dignity of not having to revolve my life around eliminating activities that I enjoy, and having to keep track of a plethora of medications that regulate my existence.

I was relieved of the burden of excusing

myself from activities because I could not tolerate one more moment of pain. It provided me with choices and the quality of life that I could no longer take for granted. I did not have to be constantly vigil about taking and calculating the simplest task for pain threshold.

I was no longer relegated to having my little grandson climb on my lap. I could actually lift him myself without any pain. I did not have to be concerned about any unacceptable side effects, like feeling drugged. That's not an option for me. With my lifestyle, I have to be able to drive and perhaps make very important decisions, even in the middle of the night.

I only needed to take one Exalgo that lasted between 24 and 30 hours. I wasn't anxious if I wanted to participate in an unplanned event, because Exalgo took more than the edge off the pain. I was totally pain-free for the first time in many years.

I sincerely hope that access to this remarkable medication will not be denied to people like myself much longer. I really miss having my life

back. Thank you very much.

DR. KIRSCH: Thank you. The next speaker is Mary Baluss.

MS. BALUSS: Thank you. My name is Mary Baluss. I am a legal advisor to the National Foundation on the Treatment of Pain. I have no financial stake in this, and my expenses have not been paid.

In addition to working with the National Foundation for the Treatment of Pain, however, I have a full-time pro bono, purely pro bono legal practice that involves the interstices of law, medicine, ethics and pain, and that inevitably revolves around opioids.

I, every day, answer phone calls. I get phone calls from patients who say, basically, "My doctor has either dumped me or won't treat me. Can he do that and what can I do?" And I get calls from doctors who say, "I'm concerned about some of my patients, and I don't know what my ethical or legal responsibilities are."

I also get calls from doctors who are concerned because they fear that their prescribing

practices will get them into trouble, notwithstanding the fact that these are physicians who genuinely and completely believe that their prescribing practices are appropriate.

There are a lot of people in pain. The Journal of Pain found a couple years ago that about 15 million Americans were receiving some form of opioids. Dosage data were not provided, and most of them were short-term, but quite a huge number were long-term.

The foundation calculates there are probably another 15 million people who would benefit from a properly chosen, properly titrated and properly monitored through medical care trial of opioids. Many people do not get this trial, and although we have DAWN data on deaths from opioids, we also have DAWN data on deaths from over-the-counter analgesics.

The key, from our perspective, is -- let me make another point about data. The Foundation's executive director has collected data from 19 years and, literally, I think, 4,000 or more patients, and found that approximately 90 percent of those, and most of his patients are on high dose opioids, about 90

percent of those were, after titration, stable on their dose for years, and he's found a tiny, tiny, tiny proportion of what he would regard as either abuse or diversion.

Often, those were involved in the titration stages. Patients were kind of self-titrating. And a lot of patients do self-titrate, and that's not great, but it's also part of the medical process, not only with opioids, but with other medications.

From our perspective, the key is access to treatment, and for many people, it's going to be medical treatment. And for many people with chronic pain, it's going to be opioids. You have the duty to oversee the safety and the efficacy of medications. You also have the duty, I think, not to make it tougher for either the physicians who are prescribing or the patients who are desperate for relief.

They're not looking for a high. You look at pharmacological data on highs, well, those same pharmacological data will show you pain relief.

I recently had an occasion to meet with some folks in the Gaithersburg library, which I'm not sure

exactly where it is, but it's not far from here. It was a meeting of the Pain Connection, which is kind of a support group for local pain people. There were about 15 people there. Four of them had brought pillows and were lying on the floor. None of them had adequate pain relief.

I recently got a call from a woman who is wheelchair-bound. She's had, as far as I can tell, every surgery known to man. And with pain medication, she can actually get out of her wheelchair and do limited, but for her, very satisfactory daily activities.

Her doctor has refused to continue prescribing her opioids. I called him to ask him why and to throw the phrase "abandonment" into the discussion. And he said, "Look, I know she needs them." This is a doctor in Cambridge, Massachusetts. "I know she needs them. I know she's benefitting from them. Her dose is high enough that it scares me. I'm a GP, and I don't have time to monitor or to learn how to monitor. So I'm not going to" --

DR. KIRSCH: Thank you. The next speaker is

Robert Lund.

MR. LUND: My name is Bob Lund. I'm from Shawnee, Kansas. I've taken a couple days off to tell you how well I responded as a test patient to Exalgo. A little bit about my medical background is I've been dealing with back pain for over 20 years. They found birth defects in my low back area.

In addition, I've now been dealing with four bulging disks in the thoracics, and have dealt with the effects of two fractured vertebrae at C5/C6, along with spinal stenosis and reverse curvature of the neck and scoliosis.

I started taking opiates to relieve pain about eight years ago, after exhausting all other alternatives. My primary medicine has been the Duragesic patch over the last several years, with fentanyl.

When I started taking Exalgo, taking one pill in the morning was incredible. To get that pain relief from morning to night, without worrying about having to have your other breakthrough medicine, is incredible. With the Duragesic, the first six to

eight hours of a new patch, you feel heavily medicated and tired. On day two, the Duragesic, you have to make sure you have those breakthrough pills, because the medicine for me starts to wear off after 36 hours.

If you forget your breakthrough pills, you better have a bed to lay down to, for myself. And then on the third day of the Duragesic, it doesn't provide any significant relief for me at all. So I change those patches out every two days.

In comparison, Exalgo evenly relieved my pain all day long, without the need of any other pills to take at the end of the day. Not only was I able to work more efficiently, but my mind functions better. I'm not as heavily medicated on Exalgo as I felt I was on Duragesic.

It's nice to be able to work and do some things in the evening, go out to supper with your family, watch your kids at a sporting event without having to take extra medicine for breakthrough pain.

So it's nice to be able to do those things and sit for one or two hours on Exalgo, which I'm unable to do without having to take the extra

breakthrough medicine that you have to take on the Duragesic.

So in conclusion, I just hope that you can help those with chronic pain by giving them the option of this medicine, because it is a great medicine. And that's all I have. If there's any extra time, I'd like to defer that time, if possible, back to speaker number three, who wasn't able to finish.

DR. KIRSCH: Yes, that would be fine.

MS. BALUSS: Thank you very much, and I will be brief. I tend to get carried away. I just wanted to say that there was no data shown today that would justify, as far as I can see, limiting the access to this medication any more than any other extended relief opioids, and I think you all -- and these comments make it clear -- understand that extended relief opioids have a very, very powerful role to play in the overall pain management structure.

Fewer pills means fewer in the purse, fewer in the pocket, fewer in then glove compartment, fewer to be stolen. It's a good thing. Pills will be lost. Addicts will misuse drugs. Those are terrible facts.

But I strongly suggest that you think about access for the patients and question whether, in fact, the REMS is maybe not more restrictive than it needs to be, and if it's going to be that restrictive in a rollout, ask over time whether doctors are not participating because of some REMS factor as opposed to some other factor.

The patients will be identified by their contracts. It may be well to have the company follow-up with the patients or have the doctors follow-up with patients, recognizing, however, that doctors do not get paid to counsel patients more than a few moments.

Most of the opioids that are prescribed, as your data show, the DEA data show, are prescribed by family practice and internal medicine people. These are GPs, basically, and they are the front line, and if you make it more burdensome than necessary -- and I leave the question of necessary up to your expertise -- then the relief will not be granted, even if it's available.

Thank you.

DR. KIRSCH: Thank you. Our next speaker is Elizabeth Turner Whalen.

MS. WHALEN: I just want to say thank you for the opportunity to share my experience with hydromorphone. I'm Beth Whalen, and I had the opportunity to come here from Kansas City. My travel arrangements were paid for.

I'm a 49-year-old mother from the Midwest, and I've suffered from chronic pain most of my life. I had an accident when I was a child, back before there were joint replacements, when they just took out your ankle joints. And then 20 years later, I was in a plane crash that broke my back. Each independently are fine, but once your gait is off and you have an upper back problem and a lower back problem, the only relief is immobility.

I'm very blessed that I've had great health coverage my entire life. It's given me the opportunity to aggressively find relief. My goal is to participate in life again, not just watch it go by. In my search for pain relief, I've used just about everything there is out there, medications, surgical

intervention, acupuncture, TENS units, a little bit of everything.

But chronic pain rules your life. It's a vicious cycle. It's not just every four hours that you have to make sure that your pain is relieved. But it also wears you down. Every three or four years, you have to find something new, because you give up.

The short pain cycle of four to six hours, you know you're having breakthrough pain. It will either wake you up in the morning or you can feel it coming on. And you'll take your breakthrough pain medication and get slightly nauseous. Then you'll be a little dizzy, then you have some relief. And then it stops working and then you know the pain is coming and it's going to return.

Then you start getting tense from that and your muscles contract and you're worried about being able to find a chair, getting home, should I be driving, because you need that long-acting pain relief. Also, all this chronic pain is fueled by emotions, social stigma, but also depression when you can't do the little things that you want to do.

My experience with Exalgo was phenomenal. My pain was under control, and more importantly, my mind was clear. There are no side effects, except constipation, but the only medication in my life that gave me my entire life back. The pain cycle was broken. I slept well. I had a clear mind. I was sharp. I got up in the morning and had a great day.

It was constant pain relief. I mean, it lasted that 24 hours. You would actually go and enjoy something and not have those pills in your pocket, because it wasn't something that you were so dependent on. I took it once a day. You didn't have any peaks and valleys, no fuzzy head, no tremors, no muscle spasms and jerks and all the funky stuff that goes on with your brain.

I've managed chronic pain for most of my life and when I was on Exalgo, I got to do everything. I didn't have to choose whether or not I should go to my son's football game, I should go to work, or go out to dinner with friends. And it used to be "or, or, or" and it would be maybe on Monday, you do something and then you save it up until Friday and then you knew

that on Sunday, you could be flat to just get the pain relieved.

Wit Exalgo, I could do everything. I went back to work full-time, which was just wonderful to use your brain and your brain was clear and wasn't fuzzy anymore.

It's not like Exalgo will let me go to a shopping mall, but I can go to the grocery store and walk -- and I don't work, I mean, I don't crash. As a parent, I'm responsible for my pain, but I'm responsible for my medications.

I need those pills, but it's my responsibility to teach my children. It's my responsibility to keep those under wraps. It's not any different than my PIN number for my credit cards or rat poison. It's my responsibility, and I'm willing to take that responsibility, because it makes a difference in your life.

DR. KIRSCH: Thank you. This concludes the open public hearing. The open public hearing portion of this meeting has now concluded, and we will no longer take comments from the audience.

The Committee will now turn its attention to address the task at hand, the careful consideration of the data before the Committee, as well as the public comments. Before we address the questions, I'd like to go back to our list of people who had questions, and the next person I'd like to recognize is Dr. Lesar.

DR. LESAR: This question is for the sponsor, and my question has to do with the actual operationalization of the REMS program and tracking. Will your system be a real-time system? For instance, if a patient tries to fill a second prescription for Exalgo, will it pick that up?

What happens about patients who might change doses? What happens if a patient leaves their medication at home and needs to have it written by another physician; that is, can they be registered at more than one pharmacy and more than one physician, and how would they know what else is going on with those types of connections?

So this has to do both with trying to reduce potential misuse, but also has to do with allowing

patients access to the med.

DR. WRIGHT: I'll ask Dr. Neuman to address your question.

DR. NEUMAN: Yes. We've built into the system certain flags, if you will, or rules, if you will, that govern some of these same scenarios. For instance, if a prescription is presented that is earlier than three days from the predicted refill date, that is, they have one prescription, it's a 30-day prescription, if it comes in before then, the pharmacist actually gets a "do not dispense" flag on the system, with instructions to clarify with the prescriber that that is their intent.

In a similar fashion, there is a flag that if the prescription -- in a similar vein, if the prescription is more than seven days late, again, the dispenser gets a flag "do not dispense," reconfirm with the patient that they're opioid-tolerant, or contact the prescriber to confirm if they're opioid-tolerant.

So we have built in there some things that will flag the system. We have -- if more than three

pharmacies are being utilized -- again, this is sequential, but if more than three pharmacies are being utilized, then we notify all the prescribers of that behavior. It could be perfectly legitimate, but it is an obvious potential flag for some diversion type behavior.

We do allow multiple prescribers because of the way group practices and things are done today. However, those multiple physicians that are prescribing still have to fall within the appropriate timelines as days dispensed. So we don't really necessarily flag on number of prescribers, but we would for early refills.

DR. KIRSCH: Dr. Morrato?

DR. MORRATO: Thank you. We're going to be asked to discuss where Exalgo lies in the spectrum of risk for abuse and mortality. So I had a couple of follow-up questions from the FDA presentation earlier.

The first one for Dr. Gong. There was some data in our briefing packet that referred to LD-50 levels, looking at the active, as well as inactive polymer that's in the product, in which we were shown

animal model data. And I'd like to get your explanation of what you believe will be expected in humans based on the dosing that's under consideration, and in particular, how these risks for lethality compare to other opiates on the market.

DR. GONG: Okay. Because this is a 505(b)(2) application, for drug abuse liability assessment, we are much more focused on the clinical data.

DR. MORRATO: So was there a reason why we were provided the table in our briefing materials? There's a claim in here that says "use of Exalgo by the intravenous route is lethal because of hydromorphone toxicity, as well as the polymer-induced cardiac necrosis and inflammation." That relates to the abuse, if someone is crushing it.

DR. GONG: Yes. The issue is there. In terms of the LD-50, it's about eight to ten times more than hydromorphone. So once they check for the hydromorphone -- 2000 is already -- they've got bigger toxicity there.

DR. MORRATO: Okay. Thank you. My second

question is for Dr. Perla as it relates to we're also asked to put the proposed REMS into context with what's been recently approved, and you mentioned a couple of precedents related to Onsolis and Embeda, as well as Palladone.

The question I have is the Palladone, they proposed limited rollout at the time of market entry, with metrics that were measured indicative of expanding market. That was not done on the Onsolis one and Embeda, and Exalgo is somewhere in between, from what we hear.

So I'm trying to understand the rationale, from the regulatory side, why there's this difference between those three drugs as to why there was limited market rollout.

DR. PERLA: Well, the different kinds of REMS we had were based on the risks that we had that we were dealing with. The rollout was -- that was before my time, so Dr. Hertz will address that one.

But as far as the Onsolis and the Embeda, the Embeda has the usual opioid risks. That's why it was put in that class, and because of the extra risks

that were identified in my presentation, why we had the more extensive REMS. So I think what we're trying to decide now is where Exalgo fits in in between these.

DR. MORRATO: Can you just explain why then -- have times changed since 2005 and so there's new thinking, or are there really product differences that we should take into account, since Palladone has the same active as what we're considering?

DR. HERTZ: Right. In terms of the rollout, that's an important question for consideration. The contrast between the rollout that was described for Palladone versus Onsolis or Embeda, there are some differences there.

So Onsolis has a very targeted patient population. It's got a fairly extensive REMS, intending to avoid what we consider the primary risk there, which is use in non-tolerant patients. It's a very, very potent product and it's really intended for patients who have a specific need.

So we think that the REMS that's been put into place by the company will address educating

appropriate physicians and ensuring that the messages get across. And the use of the oral transmucosal fentanyl products, in general, it's not comparable to the use of the oral extended release opioids in terms of distribution and numbers.

So we thought that the program for Onsolis seemed to be appropriate, looks very good to address the risks there. Whether or not this product should have a phased rollout is certainly something that we are considering, and the company offered one approach for why they haven't considered it, but it's certainly not off the table. It's something for consideration.

DR. MORRATO: So if I understand, it was because they were going after a targeted market and just its use in general already in the market, you expected it to be a more -- I guess this is for the Onsolis one -- moiré of a limited introduction anyway.

DR. HERTZ: Right.

DR. MORRATO: Right. Okay. Thank you.

DR. KIRSCH: Dr. Rappaport?

DR. RAPPAPORT: Let me just add a couple things. Just to make it clear, Onsolis is only used

for patients with cancer who have breakthrough pain. That's not a lot of patients, very limited. This Palladone, OxyContin, extended release, long-acting opiates, are used by millions and millions of patients and usually prescribed by general practitioners, most commonly prescribed by general practitioners.

I also wanted to comment on your LD-50 question. You can't really translate those kinds of findings from animal studies into humans. They give you a little bit of information, but the variability in opioids, both between patients and intra-patient in terms of the pharmacokinetics and the pharmacodynamics of these drugs is just enormous, and there's just no way to know how much of one opioid is going to compare to another one and how much of one opioid is going to lethal in a certain patient, and of course, it depends on whether they're opioid-tolerant already.

So the safety rules that we put in place are you've got to be opioid-tolerant to begin with. Then you start slowly and you titrate up, and that's the same for all of these products.

DR. KIRSCH: Did you also have a question

about the polymer and how toxic that might be if the drug was abused or injected? I'm not sure I heard an answer to that question by anybody.

DR. RAPPAPORT: How toxic the polymer would be? Maybe the sponsor would like to address that.

DR. WRIGHT: So, first, let me say that the excipients that are in Exalgo have been used in other products when administered orally and safety has been established for oral use.

I think what you're referring to is extemporaneous use or trying to prepare -- take a tablet and use it for intravenous use. So first of all, as was just mentioned, the dose that would be administered is very difficult to calculate, because of how that would be prepared from a tablet.

But based upon the calculations that we've made, trying to extrapolate from rats, that the exposure or the doses of hydromorphone and the polyethylene oxide excipients have about the same or similar exposure that would lead to a lethal outcome in rats.

Also, because of the fact that the mechanism

of toxicity is different between the two, between hydromorphone and the excipients, it's unlikely that there would be synergy in that toxicity, and it is unlikely that the excipients would significantly increase the potential for leading to a death.

DR. RAPPAPORT: Thank you.

DR. KIRSCH: Dr. Markman?

DR. MARKMAN: I have a question, again, related to the alliance program. It's currently estimated that, by one study, about 40 percent of patients who receive opioids in a primary care setting have an opioid agreement place. That number is probably higher in the specialist community, I would venture.

So what I want to understand are two things. If a patient currently has an opioid agreement with their provider and they're being rotated to this compound, would the pre-existing opioid agreement supersede the PPMA in this or would it be -- what would be the relationship between this?

Would a patient not be allowed to start this if they didn't do the specific PPMA for your drug, if

they had an opioid agreement with the primary care provider or pain clinic already?

DR. WRIGHT: Dr. Neuman, please.

DR. NEUMAN: It is not our intent for the PPMA to supplant or replace whatever existing mechanisms an individual practitioner has in place. It is our intent that the PPMA becomes a key piece of ensuring that the information that has to get from clinician to patient is actually completed.

So they may be complementary. The clinician may elect to use our PPMA versus whatever documents they normally use, but it is in no way meant to replace the normal interaction between prescriber and patient.

DR. MARKMAN: So to enroll in the alliance program, you don't need to complete the PPMA if you have an existing opioid agreement with your practitioner; is that correct?

DR. NEUMAN: The attestation of the prescriber is that all patients will have a completed PPMA.

DR. MARKMAN: Your PPMA or any PPMA?

DR. NEUMAN: The Exalgo Alliance PPMA will be completed. That is what they're committing to when they enroll in the alliance.

DR. MARKMAN: So they would need to fill out another opioid agreement then.

DR. NEUMAN: If they have their own PPMA, then they could elect to have two PPMAs. They could elect to keep them dual or they could replace it with the other. As part of the alliance, you must have a completed Exalgo Alliance PPMA in the patient's chart as part of the enrollment process.

DR. KIRSCH: Ms. Solonche?

DR. SOLONCHE: Thank you. In regard to the suggestion from one of the members of the panel that perhaps a higher price point would help prevent abuse of Exalgo, I must, as patient representative, comment that this is not a good idea on several levels.

With the ever-increasing price of medications in general, a higher price would put a greater burden on individuals with private health insurance, as well as Medicare and Medicaid, if indeed these agencies were to decide to include this

medication in their formularies.

There will always be those who will come up with ways to use medications in ways for which they are not intended. Let us not put the additional burden of increased price on the people who need appropriate medication.

DR. KIRSCH: Thank you. Dr. Zito?

DR. ZITO: I'd like to go back to the issue of efficacy and safety, because I see a huge disconnect here in terms of the data that you -- the study that you presented and what I imagine would be grounds for making this more-abusable substance available; in other words, that the severity of illness would be a driver.

So initially, when I was reviewing the materials, I was understanding it differently. I was expecting a study that would address people who were opiate-tolerant only, and yet that's only half of the sample that was selected.

I was expecting people that would have more than moderate osteoarthritic pain, because that's a huge, huge pool of individuals. So other problems

relate to concomitant drug use and the potential for serious drug interactions, and also, at the time of exposure, there were very few people that had long-term exposures here, and as has been pointed out earlier, a big drop throughout the trial.

So in the absence of -- and the point that the effect size appears to be rather small and we don't have analysis that deals with number needed to treat or number needed to harm. It's hard to get a fix on where the benefits are that will then justify this elaborate safety system that you're suggesting be put in place, and at the same time, it's got lots of limitations, which other people have spoken to.

So I wonder if you could give me a better feeling for why this is adequate efficacy information.

DR. WRIGHT: Just a couple points that I wanted to mention before Dr. Gallen addresses your question. That is, I think you said -- you mentioned osteoarthritis, but Study 301 was in low back pain.

One other comment I think you mentioned is it was only half opioid-tolerant, but they were all opioid-tolerant in that Study 301. Dr. Gallen?

DR. GALLEN: I think you raise a number of important points and I think that they're worth addressing. As Dr. Wright noted, this was in opiate-tolerant patients, because that's where we really see the need. That's where we really see the impact and the best benefit-to-risk ratio with this drug.

In terms of the severity, patients will vary, obviously, as to whether I will call my pain an eight or a nine or a ten. So there's some noise in that. You find a good mix basically between seven and going out to the high nines, which is the moderate to severe pain category.

I think as you can tell from the people that you've heard from in the audience, whether one categorizes pain as a seven or an eight or a nine, it's quite impactful on their life. It's quite meaningful to them, and our obligation, I think, is to develop therapies to address that need.

In terms of concomitant medications, one of the nicer things about hydromorphone as an agent is that it doesn't have a lot of significant P-450

interactions. I think that's one of the reasons why it's a good option for patients who have more complex medication regimens, where P-450 interactions can cause inductions in metabolism of their drugs.

So we think that in terms of concomitant medications, we're in relatively good shape on that. In terms of the effect size, again, the effect size was an effect size that the patients themselves basically classified as good, very good or excellent.

I think that the patients are likely the best judge of what the meaningfulness of a given effect size is. Our effect size is basically the same level that one would get from another opiate in a comparable trial.

But really, at the bottom, the bottom line on this is that every human being is individual. There are people who will respond very well to morphine, but, say, not to OxyContin or vice versa or to hydromorphone.

What we're really seeking to do, as you can remember from the key chart that Dr. Webster put out, is to provide for those patients who respond well to

this medication. I think you heard from a few earlier. For those patients, to provide them with access in a way that's not an undue burden to get the access, but to be able to get their lives back. And that's really our purpose in this.

DR. KIRSCH: Thank you. Mr. Yesenko?

DR. YESENKO: This is a comment about Dr. Gong's presentation. Dr. Gong, would you mind addressing the fourth part of your conclusion, the sponsor's data indicate a high level of drug accountability?

DR. GONG: Thirty-six percent of drug accountability is high. I have several issues here. First, as a Schedule II substance, it is supposed to be very low, no drug accountability.

The second issue is the data I presented is only part of the selected data. The sponsor has an algorithm of 5-plus-5 to pick up the part of the patients that have the drug unaccountability problems.

We are still waiting for more than 200 narratives of the patients with drug unaccountability issues to analyze. Finally, the clinical trial is

very strict. So nothing more strict than a clinical trial. So if drug unaccountability in a clinical trial is so high, we think they will most likely have a much more high level of drug unaccountability in the general clinical practice.

DR. YESENKO: Who are you waiting for the 200 narratives from?

DR. GONG: Say it again.

DR. YESENKO: You're missing 200 narratives.

DR. GONG: Yes. We are waiting for, yes.

DR. YESENKO: Where are they?

DR. GONG: The sponsor is still doing the writing.

DR. YESENKO: Then this would be for the sponsor. How long would that take?

DR. WRIGHT: Those narratives that he's referring to, we just received that request for those, I believe, a week or so ago, and they are going to be delivered on October 2nd.

DR. YESENKO: It would have been timely to have those here. And then the next comment would be for the training of the physicians who will prescribe

Exalgo, do you have training requirements, like the buprenorphine physicians have an eight-hour requirement to prescribe buprenorphine?

This is for the sponsor. Will you be having a minimum training requirement?

DR. WRIGHT: Before we get to that question, I'd like to address that question about accountability, if we could.

DR. YESENKO: Please, yes.

DR. WRIGHT: Thanks. Dr. Gallen?

DR. GALLEN: Yes. I think that the accountability issue is important to address. Dr. Gong did an excellent analysis, that we agree with. We think it was accurate as performed in showing that those patients who were already selected to be the most discrepant population, when measured in the way that he measured them, which was to look at what percentage of the drug you should have returned were returned, showed very high numbers of accountability -- of drug discrepancy.

There's two important things worth nothing. First, in terms of that way of calculating it, if a

person was given 100 tablets and they used, appropriately, 90 and they were supposed to return 10, being discrepant three out of 100 tablets, by that method of calculation, would be a 30 percent rate of discrepancy, because they were three out of the 10 that they should have returned.

That's a perfectly legitimate way to look at the data, but it produces very large percentage numbers that can be misinterpreted. Another way of looking at it sort of in the big picture across the trial is basically about 64,000 tablets were dispensed in the course of this trial. About 2,400 tablets are discrepant at this period of time, not having completed all of those narratives yet, about 2,400, which is about 3.7 percent of the medication in the trial.

Now, we take that 3.7 percent very seriously, and we're engaged in an effort to try to understand exactly where that went. What we understand at this point were the points that I made in the beginning of my presentation; that patients with positive urine drug screens, if your average

completer has a discrepancy of about four to six tablets, patients with positive urine drug screens, the worst of that group are up to 30 tablets. It's much, much higher rates.

Patients who fail to show up, even if it's -- fail to return their medicine or if they lose their blister pack, even if it's entirely innocent, show up with very high rates of discrepancy.

So the bottom line is that discrepancy is an important signal, and we're addressing it in a serious way, but we want to understand, in terms of the overall trial, we're talking about a few percent. We're not talking about 30 percent or those kinds of very large numbers.

DR. YESENKO: I think you're missing my point. For this purpose of this meeting, we are to look at the safety and efficacy of Exalgo, and those 200 narratives would have been very helpful to look at to get a complete picture.

Now, for the sponsor, would you address the training for the physicians that will be prescribing Exalgo?

DR. WRIGHT: Yes. Dr. Neuman?

DR. NEUMAN: There is mandatory training of the prescriber as part of the enrollment process for the Exalgo Alliance.

DR. YESENKO: Thank you.

DR. KIRSCH: Dr. Lorenz?

DR. LORENZ: Just a brief point of clarification with regard to pricing issues. I just wanted to assure others that I wouldn't advocate for any particular approach. In fact, I think the question of how pricing might affect the patient's cost is a function of several things.

First of all, it's not clear that the distribution of cost rather than total cost wouldn't be one effective strategy. So that needn't necessarily affect the total cost over the course of an episode of illness, for example, that a patient might face.

Furthermore, the question of cost with regard to drugs is very much dependent on who the payer is, and while certainly, we would want to affect the patient's incentives, that also depends very much,

of course, in our current society, on insurance status.

So I think those are empiric questions, and I would not want to discourage testing pricing strategies empirically as an effective deterrent, especially since, in general, the conceptual idea that incentives should target those whose behavior is in question is something that I would want to endorse.

DR. KIRSCH: Thank you. Dr. Vaida?

DR. VAIDA: Yes, for the sponsor. I guess it's probably just one question, but with the transition of care, with the acute care and the ambulatory care, and going along with REMS and trying to track the medications and if the patient doesn't come in for -- or if they come in too early for a refill.

I guess the first question is, is the drug going to be available in 100 milligram tablets rather than like unit of use, 30, 60, 90?

DR. WRIGHT: You mean the tablet strengths are between 8 and 32 milligrams.

DR. VAIDA: No. The total number of tablets

in the bottle, the package size. I mean, your label says 100. You just mentioned like if the patient got 100 tablets, but they didn't return 10.

Since we're looking at 30-day supplies -- I'm just curious. Is that the way it's going to be available, the package size is going to be 100 rather than unit of use, like 30s or 60s?

DR. WRIGHT: The package will be bottles of 100 that will be provided to the pharmacies.

DR. VAIDA: And are there any plans to make unit dose available for patients that may go on the inpatient side?

DR. WRIGHT: I'll ask Dr. Neuman if he would address that.

DR. NEUMAN: We have looked into having some kind of unit of use packaging, but that's not currently what we're asking approval for of the FDA. It's the 100-count bottles. But we certainly see there could very well be a need to supply it in that form.

DR. VAIDA: How is it available in Europe? Package size.

DR. WRIGHT: I'll ask Dr. Richarz if she would address that.

DR. RICHARZ: It differs from country to country, but there are smaller package sizes available.

DR. KIRSCH: Thank you. We're going to now move to addressing the questions posed to the Committee from the FDA. And the first question, which will show up on the screen here in a second, I'll read.

It says to discuss where Exalgo lies in the spectrum of risk for abuse, including abuse-related overdose and death, compared to other opiate drug products.

I'll open the floor for comment and discussion for the members of the Committee. Well, then, I'll call on somebody. What I heard from the public hearing was the outcry, as I hear it, to recognize the risk associated with this drug, but also not to make it so burdensome to patients who need the drug.

So I'd like to ask maybe one of the patient

advocates to comment on your perspective, please.

DR. YESENKO: I think Dr. Gong's conclusions hit it on the head. I mean, hydromorphone has a high abuse potential, at least comparable or slightly higher than oxycodone deaths. And then he bolded the statement, "In summary, these data are predictive of high levels of abuse and diversion of Exalgo." It still is an opiate. There is still risk for abuse, whatever form it is.

DR. SOLONCHE: As I've already said, people can always find a way to abuse a drug. Whether the way this pill is constructed will make that easier or harder, I don't know. I couldn't possibly speak to that. I couldn't possibly speak to that.

DR. KIRSCH: Dr. Vaida?

DR. VAIDA: I guess just from a medication safety standpoint, if you want to just expand that abuse potential, I mean, our experience with our organization is that hydromorphone is a really misused drug, misdosed drug on the acute care side.

It accounts for a lot of patient harm, a lot of fatalities, especially in the last couple years

because of the equipotent doses. But that's more on the prescribing side, if you want to say, from an abuse.

But why that would change on the outpatient side compared to some other opioids that may be more closer to the potency -- we learned from fentanyl. When fentanyl became available as a patch, we received a lot of errors. The FDA had to backtrack and come out with a black box warning because of the equipotent doses.

So I guess the only thing from a hydromorphone standpoint, knowing our experience on the inpatient side, that the injectable -- a lot of patients get harmed, because it's a dose at the same dose almost as of morphine, which it's not.

I think there is a lot of concern on if now it's available outpatient-wise, that people are going to be using or prescribing -- prescribers are going to be prescribing "not exact equipotent dose" compared to what patients may have been receiving on some other long-acting opioid.

So if somebody is on 60 milligrams of

morphine a day, they may be looking at starting at the 32 milligrams, not the one-fifth of that. So I think just from the experience standpoint from our organization, that the drug itself, because it's not a one-to-one with some of the other products available on the marketplace, does have a high risk, that the risk is high.

DR. KIRSCH: Dr. Morrato?

DR. MORRATO: I just wanted to add to that. I think, also, we heard, in terms of the DAWN data, although it has its limitations and is imperfect in some areas, would suggest that, given the drug abuse ratios that were there, that what we saw with the immediate release hydromorphone was on par with the extended release oxycodone in terms of some of those measures.

So that would be supportive of what we've been saying, that it's at least equal to or greater than in risk to the other opiates.

DR. KIRSCH: Dr. Covington?

DR. COVINGTON: I guess there's sort of two different ways to look at it. I think the kinetics of

the product, the fact that you get a Cmax at six hours suggests that it's probably not going to elicit addictive or abuse behavior in people who don't already, in the same way that putting on a nicotine patch doesn't elicit abuse because it takes forever for anything much to happen.

On the other hand, I haven't heard anything to suggest that for those who are seeking recreational use or for those who already have an addictive disorder, that this will be appreciably different than sustained release oxycodone.

We've known for many years that hydromorphone is a drug with very high street value, very high liking. People like the drug. And I think it would be reasonable to predict that the abuse of this product will closely parallel how much of it there is in the system, how much there is in grandmother's medicine cabinet.

I think if there's a lot out there, we'll see the same sort of abuse with this that we saw with OxyContin.

DR. KIRSCH: Dr. Denisco?

DR. DENISCO: From, of course, the data we've been presented, it corresponds very much with clinical experience that Dilaudid is pretty much the end of the line. It's very potent.

However, it has no more dangerous overdose than immediate release anyway. Hydromorphone has nothing worse than oxycodone, which is out and available. It's a very potent, very powerful drug, with a very high subjective liking on the part of addicts, but all these opiates are.

Plus, this drug is only being advocated here -- or indicated, not advocated, but indicated for opioid-tolerant patients. So you're sub-selecting a group out, and probably these individuals would have been tried on possibly other drugs before this.

So I don't see anything to make it any worse than oxycodone, or any significantly worse than oxycodone.

DR. KIRSCH: Dr. Zito, do you have a comment? Go ahead.

DR. ZITO: I'm not familiar with pain management in general. So I'm wondering what

physicians do when there's a long-acting drug on board and the patient is in obvious distress from excessive respiratory depression.

What are the options, and how much does that require really close monitoring in order to be effective?

DR. KIRSCH: I'm not sure that either the sponsor or the FDA can answer that question.

DR. RAPPAPORT: Well, we do have some clinicians around the table who could address that, I think.

DR. MARKMAN: I think it's most important to recognize that in an opioid-tolerant patient who is using chronic relatively high doses of opioids, 60 milligram morphine equivalence or greater, the risk of respiratory depression with appropriate use is vanishingly low.

I don't think that's something that we're challenged with as the main issue here. So I think from a clinical perspective, that's not a really challenging problem. It's the other side effects, which we saw in the data, which are, I think, more

vexing for most patients and tend to be what we call the dose-limiting opioid toxicities. That would be nausea, vomiting, constipation, sedation.

Those would be the leading issues in terms of what challenges, higher doses, and better pain relief as opposed to respiratory depression in an opioid-tolerant patient receiving chronic opioids.

DR. ZITO: So the assumption then is that you would know the level which they can tolerate of this new product that they're going on to; that you have enough prior information on their exposure, right?

DR. MARKMAN: Right. I think the indication we're discussing here is not for opioid-naive patients. We're assuming here that all of the patients who are going to be tried on this medication are going to be opioid-tolerant if they're doing it as it's designed. So that risk would not be the risk I think that was really the one to be most concerned about at all.

DR. ZITO: The reason I bring it up is that in looking at the surveillance data on mortality

events, you had elders, Alzheimer's people, and you had very, very severe respiratory depression.

Now, I don't know -- with case reports, we don't have usually a good enough story. But I'm wondering how the prescribing doctor is going to -- is he or she going to have the necessary baseline information that would allow you to say that I know that starting this person on whatever, 16 milligrams of this new product, is going to be a tolerable one?

DR. MARKMAN: Again, I welcome others to comment, but these would not presumably be opioid-naive patients. They would be opioid-tolerant patients, and you'd probably be rotating, and we've heard a little bit about opioid rotation today.

Certainly, there are -- to your point, though, which I think is a very important one, there are certain sub-populations of patients in whom we have a greater level of concern about respiratory consequences of long-acting opioids. Those are patients with underlying pulmonary disease, patients with obstructive sleep apnea, and other conditions which I think would cause -- or patients on other

sedating medications or patients who are heavy users of alcohol.

So if a patient is on a benzodiazepine or a drug of that type, in that category, which is going to cause respiratory suppression, there is going to be, as you would suggest, more concern about the potential consequence for a synergistic effect which would be adverse.

DR. KIRSCH: Dr. Rappaport?

DR. RAPPAPORT: I'd just like to add that those risks are inherent with all of the potent opiates, and the way that we've addressed them thus far is with the label and prescribing information for physicians, and I think that is a different issue than what we're trying to focus on today, which is the issue of misuse of the products, but as Dr. Markman was saying, in ways that affect people due to accidental exposure and diversion and abuse and addiction.

The really severe safety issues with these products are, I think -- and I'd like to hear if other people around the table think differently -- probably

as well-controlled as they can be with the current set of warnings, when used by physicians who read the warnings.

DR. KIRSCH: Dr. Denisco?

DR. DENISCO: Just to finish that, I would agree completely that these are all potent drugs, but they're all very similar, and I guess that's what I'm thinking of.

The discussion, to me, is almost sounding like this is like a new drug. I don't see much of a difference if somebody takes two 8 milligram immediate release versus one 16 milligram and chews them both, and it's the same dosage of the same medication.

There's been no implication that this route of delivery is safer, but rather, it's more convenient and possibly safer, because you have no big peaks and troughs for the patient taking it, but it offers no abuse deterrence at all.

I don't see it as anything different than the immediate release formulation in a larger single dose. But there would be less pills available, too. So it really seems very similar to me.

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: I have to agree with the comments made before, including Dr. Rappaport's, to answer the question about where the drug lies within the spectrum of risk. I think it's similar to the other opiates that we're discussing and we have mentioned. So I don't put this at a higher risk than some of the other potent opiates.

I do have a concern with this, as well as other medications for oral use that we've discussed and I think ought to be addressed between FDA and the sponsor, and that's the misuse, and I focus my attention on pediatric patients.

So packaging, dispensing and limiting the total doses available for misuse is an important one. I empathize wholeheartedly with all of the public comments that were made, and I think it's important to note that most of the speakers had talked about their families.

At the same time, I am concerned about the children in those families, and the fact that this is a potent medication and how it's appropriately

dispensed is correct.

The comment about whether the general practitioners are the most likely to dispense this, I'm not sure that we can restrict this, and I don't know what authority we have to restrict practice of medicine and who can prescribe Class II medications.

Dr. Rappaport, I don't think that is up to the FDA. Is it state-specific?

DR. RAPPAPORT: We generally have not, in the past, restricted to specific prescribers, and probably will not do so in the future.

DR. KIRSCH: So I'd like to summarize the comments, as I heard them, and I'd be happy to have an edited version of what I'm about to say, if you think I misrepresent what the summary is.

But I think we've heard that the drug Exalgo is a highly efficacious drug for a group of patients who are in pain. But in addition to that, it also has significant potential for abuse because of its liking, its effects that it has.

So on the spectrum of risk of abuse, I think it's towards the top of that spectrum of the drugs

that we currently have on the market.

Is there any request to edit that comment? Dr. Lorenz?

DR. LORENZ: I think my clinical experience tends to make me want to endorse “highly efficacious,” but the trial that was presented actually mutes my enthusiasm a little bit, at least in the patient population in which efficacy was demonstrated.

DR. KIRSCH: So I'll use the word “significantly” efficacious. We're going to go on to the second question, which is in front of you now. Based on your assessment of the risk associated with abuse of Exalgo, discuss which of the following options would be appropriate for risk management; first, a program similar to Onsolis, including registration for physicians and patients; second, an opiate class-like program, including physician education and registration, but no patient registry, and in the short-term, an interim REMS pending larger opiate class program, as was done with Embeda; or, third, a unique program that was not yet described here. I open this question up for discussion.

DR. MORRATO: Is one of the options what the sponsor presented?

DR. KIRSCH: I think that option is in B, which is the short-term and then follow-up. Is that the intent of the FDA?

DR. RAPPAPORT: No. Actually, I think -- I mean, there are little differences between the programs, but I think it's probably closer to A, the sponsor's program.

DR. KIRSCH: Dr. Vaida?

DR. VAIDA: I mean, they said that there was really no patient registry, right? That they actually specifically stayed away from a patient registry.

DR. RAPPAPORT: Well, it depends on -- there's a lot of problems with the definition of registry. They are registering their patients in order to keep track of who is getting the drug, and that's part of their program.

There's a difference between what somebody else was saying earlier about registering patients in order to collect information about how they're doing. So it gets fuzzy in there, but they have a patient

registry in their program, as does Onsolis.

DR. KIRSCH: Dr. Covington?

DR. COVINGTON: Just a question. It seems to me that we've agreed with the not-too-surprising conclusion that hydromorphone is an effective analgesic.

DR. KIRSCH: Thank goodness, we did.

DR. COVINGTON: We were right on the ball. And it seems, I think, that we're in agreement that it's not any more dangerous than any of the other long-acting opioids, probably safer than methadone, for example.

My question is, is there a time to discuss the question of what do we gain by making all of our short-acting opioids long-acting if we're not doing anything to make them less abusable and less lethal in overdose, and less propensity for kids to take overdoses of them and such? I guess that's what I'm dancing around.

DR. KIRSCH: Maybe the FDA could address that question.

DR. RAPPAPORT: Actually, I think sort of

the crux of the question here is the value of having the benefit of a long-acting product to the patient, which clearly has some value, as you've heard and as you know yourself.

Does that outweigh the risks to the society of probably increases in deaths and addiction? And that's sort of the question we're putting to you. Does that benefit outweigh that risk. And also, how can we manage that? So that's what's on the table.

DR. KIRSCH: Dr. Denisco?

DR. DENISCO: Just in response to that, I guess with this particular medication as opposed to oxycodone, where it was hard to abuse oxycodone, because in my understanding, it only came mixed with Tylenol or aspirin -- I'm sure there was a form out there back then, but it wasn't widely used, at least in my circle.

Then when you put oxycodone by itself with a lot of milligrams, it was highly abusable. But I don't see the difference in this with, again, two 8 milligram pills or one 16 milligram pill. It just doesn't seem like there's that much of a difference.

But just a comment on this. I see a real difference between immediate release oxycodone when it's formulated with Tylenol or aspirin versus pure 80 milligrams in a tiny little pill.

The thing I did want to ask about the registration, because I was also confused about where the sponsor fit in these questions, was I know there are HIPAA rules. Certainly, anybody who has wrestled with implementation of that knows that we're talking about creating -- registries being created.

Where does this fit within the already existing HIPAA guidelines? I assume that the legal thing that was presented for the REMS doesn't supersede HIPAA. So I'm just kind of wondering that. Will the making sure we account for HIPAA determine how the registries really have to be conducted?

DR. KIRSCH: Would the sponsor like to respond to that question?

DR. RAPPAPORT: While they're getting together over there, could you just clarify, Dr. Denisco, when you were saying you don't see much of a difference in the way this product is versus the

short-acting, do you mean in terms of risk?

DR. DENISCO: Yes. In terms of risk, oxycodone was a real sea change, because we went from having tablets that maybe had 5 milligrams of oxycodone with 325 milligrams of aspirin or acetaminophen.

So it was very hard to abuse those 5 milligram pills. The patient could take more of them, of course. But then when oxycodone was packaged in a small, easily crushable, snortable and injectable form, without the mixed aspirin or acetaminophen, it became a very abusable substance because of its formulation.

This formulation does not appear, to me anyway -- I mean, we all agree it's a high-risk drug, but it doesn't appear that this formulation is any worse than the immediate release formulation.

DR. KIRSCH: The sponsor?

DR. STEMHAGEN: I'm here to answer the question about HIPAA.

DR. KIRSCH: Yes. The registry and how it relates to HIPAA.

DR. STEMHAGEN: So there are a couple of things. One, there is a HIPAA statement on the patient form. So they are told that the data will remain confidential, and of course, there is always the HIPAA relationship between the patient and their physician, and that's independent of this.

Can we get the slide up? Maybe we can't get the slide up. I can just tell you what the slide says. In terms of the -- there it is, okay. There is one database where all of the enrollment information gets included for the prescriber and for the patient.

So patient-identifiable data are saved in a separate database from the clinical data. So we always maintain that separately. The private patient information is de-identified in the system and it's encrypted in the database. So even database administrators can't read the data.

The database is secured and there are only certain people within the group that's working on the system that actually have access to it. So there's limited access. We have a secured connection with individual user names and passwords, and the system is

compliant with all HIPAA and Health and Human Service database requirements in terms of maintaining security.

DR. KIRSCH: Dr. Morrato?

DR. MORRATO: I was trying to reflect back on the question, or trying to rank or place where does this risk management plan relate to the other options, and I wanted to comment.

When I look at Onsolis, there's a couple of -- tolerance to opioid therapy is one of the considerations for that. It sounded like that that was driving maybe that kind of form of plan.

I would agree that the Exalgo one is fitting more in line with Onsolis. The other piece that Onsolis, while it may not be a prescribed rollout the way it was with Palladone, in effect, it's a limited launch because of the indication and the type of use.

I haven't heard any data that would suggest that since the Palladone launch in 2005 and now, why we wouldn't employ that same kind of principle of at least having an immediate rolled-out, phased launch in which you're going to perhaps the pain centers where

the types of patients that we heard from are more likely to be treated, and test these systems and place an evaluation, make sure things are working before you just go to the masses with it.

So perhaps there was other data that I missed that would suggest not to do that. But if it was a good idea in 2005, I don't know what's changed necessarily to move from that.

DR. KIRSCH: Dr. Lorenz?

DR. LORENZ: Just to address a broader question of whether these kind of medications offer benefit versus their risk profile and other similar long-acting opioids.

Just to speak as a clinician and to put aside other hats that I sometimes try to wear, I just want to say that in palliative medicine, in particular, although the data that was presented today doesn't necessarily address that population, my expectation is that it will be highly useful to patients with cancer pain and patients in hospice and palliative care, for whom we often, often need additional options, and for whom the addition of a

long-acting opioid is an extremely important step.

I could certainly expand on that comment, but I just wouldn't want any other concerns to highlight the fact that my expectation is that this will prove highly beneficial to such patients.

DR. KIRSCH: Dr. Vaida?

DR. VAIDA: Probably as even a follow-up to that, although I had a couple other comments, one with Dr. Rappaport. I really don't agree that the education that we have in place on the use of a lot of these medications is adequate.

I go back to the injectable hydromorphone. This is a huge issue in acute care. It's a huge issue because of the way it's dosed. And going with the comments we just heard, I mean, in the public comments, this drug seems like it does have a place in therapy, just like anything else, as long as it's dosed properly.

But one of the concerns is because of the potency of this drug, and I'd say, again, what we've learned with transdermal fentanyl, we had major issues. We're trying to equate those potencies in

patients that probably didn't fall within the realm of using that drug.

Everything I've heard on the REMS so far, trying to get into this question, there's a lot of pages on it, but there really isn't anything real tight, such as if a prescriber doesn't prescribe the way it is, that's a prescriber-patient relationship, or how they're going to follow-up.

I didn't have a good feel for that. Even enrolled pharmacies, being a pharmacist, I mean, there's a pharmacy representative that signs. Well, does that mean that if I have a chain pharmacy and I have 12 pharmacists, there's that one representative that signs and that person is responsible for training 12 other people?

I'm just not real convinced that it's a real tight program on monitoring where the patients -- or that patient population is, although I really do feel that the drug has a place in therapy, and it has had it for a long time. But it's that equianalgesic dosing that really has me concerned.

DR. KIRSCH: Dr. Markman?

DR. MARKMAN: I would just like to underscore Dr. Lorenz's point. Obviously, the compelling presentation of Dr. Webster and what we heard from the patients today, I think that hydromorphone has analgesic efficacy, and there is a significant subpopulation of patients with chronic pain of moderate to severe intensity who will benefit from having this option, and as a clinician, I would welcome having this option.

That being said, I think that the REMS program, as currently proposed, as has just been said by Mr. Vaida, frankly, is somewhat vague. The expectation that opioid agreements, or here, as they're called, these PPMAs, are going to change the current curves that we're seeing from the DAWN data and anything else, since they're widely in use already, I think is unrealistic.

Certainly, the trends do not suggest that using opioid agreements is changing that pattern. It's incredibly important. It's a valuable educational tool.

I commend the sponsors for making

stakeholder education and the PPMA essential pillars of their program. I think that's the right thinking and I applaud that. But I don't think that is enough, quite frankly, to attenuate the trends that we're seeing. So I think more needs to be done than just that.

To Dr. Morrato's point, I think a phased rollout would be one way to understand how this will play out in a larger population, such as the population of patients with low back pain, which, as we all know, is the largest population of chronic pain patients in the United States, and it's a very heterogeneous population.

So I think it would be important to see how that plays out in a more-restricted environment before exposing it to a broader market. And I think one way to do that would be to have a registry, to use the word that's already been used, that was tighter, where we had a better understanding of who was using the medication and what they were doing about obvious cases of abuse, misuse and diversion, because I think those are the three different issues here that really

need to have a REMS program to focus on, and I'm not clear that the one that's proposed is sufficient.

DR. KIRSCH: Dr. Zito?

DR. ZITO: I would second the comments that were just made. I think that very clearly states some of the concerns. I also want to go back to Dr. Morrato's comment about Onsolis, because I was impressed with it, but also because it's a much more selected and, I think, narrower patient population than is being proposed.

So without more criteria to understand the criteria for being opiate-tolerant, for example, operationalizing some of those criteria or by setting or by specialty, et cetera, would help, I think, to narrow down the scope so that you're getting at the people that you know are the intended population.

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: Just to echo the comments that have been made, this is an important drug, and they can add another potent tool in the armamentarium. I think the challenges, in response to the question, if I look at the question, when you say similar to

Onsolis, I would add that the REMS program, as described, may be similar, but a lot of things that were just discussed need to be tightened up, including what we had discussed during the presentation, which is external review.

As proposed, the periodic review is an internal one, and in order to avoid conflicts of interest or perspective at some point, I think the sponsor addressed that as something that they would consider, would recommend that that is included in the REMS program to go forward.

From the standpoint to respond to the public comments, this is a deliberation to make sure that a medication that most of the clinicians here have said is useful stays on the market, because if it comes on the market and the REMS program is inappropriately rolled out, then people will be harmed, and we will be forced to then recommend taking it off the market.

I think that in good conscience, with clinicians sitting at the table, we want to make sure that the rollout of a drug that can be helpful is really helpful to the people that need it.

DR. KIRSCH: Dr. Jenkins?

DR. JENKINS: Thank you. As I've been listening to the discussion about question two, I feel like it may be important to clarify what we're actually asking you to comment on in question two.

As you know, we announced in February of this year that we were going to have a REMS for all the extended release and long-acting opioids. That program is not in place yet, and it's taking some time to develop that.

In the interim, we have products that are coming through the pipeline for us to review that we have to decide what to do with them as they're coming, while we're in parallel working on this class REMS program for the extended release and the long-acting product, which is methadone.

We've segmented those off as a class that we think needs to have a REMS to ensure that the benefits of the drug outweigh the risks.

The oral transmucosal fentanyl products have been segregated off into another class because of their unique indication, their unique risks, et

cetera. That's why the Onsolis approval has a fairly restrictive REMS program, much more restrictive than what is currently in place under the voluntary risk management programs and the interim REMS that was approved a few weeks ago for Embeda.

What we're really asking you to help us with is we now have extended release hydromorphone in front of us. Normally, it would go into the extended release, long-acting class that we've identified. If you just think about it from the perspective, it's an extended release product. It's not an oral transmucosal fentanyl.

So normally, you would think, well, that would be something similar to what we did to Embeda. But we know that there are these concerns about the abuse liability potential for hydromorphone, and that's why we're asking you to help us understand. Should we treat this like Embeda and the other extended release opioids pending development of the class REMS, which would cover all of them, or should we consider it to be a higher-risk product and have something along the lines of Onsolis?

The program the sponsor is proposing is significantly more restrictive than what's currently in place for Embeda, OxyContin and the other extended release products, while we're waiting to develop the class REMS.

So we're looking for your advice. Should we approve Exalgo with a program like Embeda, an interim REMS pending the class REMS that we're still developing, or is it so unique and different and higher risk that it needs something above that, maybe more like Onsolis, which is actually kind of what the sponsor is proposing?

Mixed in with that, you have to understand that under the statute, we have to determine that the provisions of the REMS are required to ensure that the benefits outweigh the risks. So we have to determine that the restrictions we put in place are required to achieve that goal, and if we can't determine that they're required, then we can't require them.

So we're really looking for you to help us understand. Is this different from the other extended release products, such that we should treat it

differently as we go forward to thinking about whether it should be approved?

So hopefully that helps you understand. Sponsors can do more, if they choose to, voluntarily, but if we're going to use the statute to require them to have a REMS, we have to be able to articulate and defend legally why those programs are required to ensure that the benefits outweigh the risks, which is a statutory standard.

Again, what the sponsor has proposed is more restrictive than what's currently in place for Embeda, which was just approved a few weeks ago, and the other extended release products, while we're developing the class REMS.

I can't tell you yet what the class REMS will look like, because we're not final in developing that, and there will probably be future public discussions to get input before we'll finalize that program.

But hopefully that can help you clarify. We're asking you to help us understand. Is there something unique about this product that says we

should be much more cautious and much more restrictive than the other extended release products? Hopefully, that helps to clarify the question.

DR. KIRSCH: Thank you. Dr. Flick?

DR. FLICK: Notwithstanding Dr. Gong's comments, there's nothing that I have read or seen that convinces me that this formulation is unique with regard to abuse potential. It would seem that any of the extended release formulations have roughly similar potential for abuse and misuse.

I think it's concerning whenever you package such large amounts of narcotic in a single vehicle, and it concerns me that rolling out this drug -- as the sponsors have said, the primary risks are overdose, abuse and diversion.

It would seem to me that overdose early in the rollout of this product is going to be the primary problem. And I would wonder whether actually a lower dose should be rolled out rather than -- and I think the sponsor has, by eliminating the 64 milligram size, has recognized the concern of large amounts of narcotic in a single tablet, that one should consider

reducing the tablet size even further on the initial rollout.

With regard to the questions that we're being asked, I think that's complex. I think the sponsors have provided a reasonable approach to rolling out the product that's more restrictive than others, and I think what we should do is consider adopting what they have said, with modification. And as the FDA pursues a broader strategy, we may use that as a model.

DR. KIRSCH: Dr. Lorenz?

DR. LORENZ: Yes. I'd like to speak directly to your comment, in that I don't believe that the risk is substantially higher with this medication than other products, and I do think the benefit for subpopulations may be quite substantial, more so than for the broader population that was illustrated in the data presented.

But I am concerned about the REMS and our enthusiasm for allowing a more complicated procedure to perhaps be a proxy for effectiveness, or mislead us into thinking that the REMS might simply be more

effective.

First of all, in populations where there's substantially more benefit -- and, again, I have to speak to the cancer population that I frequently work with -- I think there should be consideration to tiering REMS, in that in settings where the benefits are high and the risks are low, because the patients have such short life expectancies already, that we should be really cautious about raising the barriers on providers in particular, and reducing or impairing access to those medications.

So it's not clear to me that one size has to fit all in the marketplace, even if one size fits all for the class of opioids.

The other issue that I really want to address is that it's still unclear to me that the registry will product effective data about which REMS strategies are effective. And I guess the challenge here is always kind of a unit of analysis problem, and can we really say, when a prescription was dispensed, that it resulted in a certain action, and I think that's really something that the FDA should address.

I don't see the creation of registries as punitive. I think there's a lot of unknown information here about exactly what steps are going to be effective and it will take some time, both for this drug and other drugs, to figure out what really works in terms of REMS strategies.

But unless we can track the progress of these medications from their point of dispensing to their eventual use, we won't have these answers. That means that we have to have registries, or at least subsets of registries that are detailed enough to give us meaningful clinical information, and I have not yet heard that anyone is going to invest in creating that sort of reporting structure around this or other opioids, but I think it's really essential.

DR. KIRSCH: Dr. Covington?

DR. COVINGTON: Just to comment on other things, I don't think there's any reason to think this is more hazardous than other sustained release preparations, and it's certainly an important addition.

I guess what I like about the registry, as

proposed, is that it seems to me that a lot of the kind of egregious behavior that occurred with some other medications in part was the result of a cavalier attitude on the part of patients and physicians.

I like the idea that the physician who prescribes this will know that, in a sense, someone is looking over his shoulder. The patient will have the same sense.

I just think the fact that people are aware of that vigilance -- it's an empirical question -- that it could result in significantly less abuse. So I like that part of the REMS. I kind of agree with what Dr. Lorenz said in terms of making the registry actually useful.

I am troubled by the hassle factor. It seems to me that the REMS involves enough of a hassle for a prescriber and a patient that that would automatically make it your last choice, just because it's a pain to do it. So that's something that concerns me.

DR. KIRSCH: Dr. Denisco?

DR. DENISCO: I have a certain kneejerk

reaction to want to do what appears to be safest, but what appears to be safest, experience has taught me, due to unintended consequences, is not always in the best public interest.

I am just not sure that the program is so complicated, it seems like it's going to be unworkable. I would not want to have a national rollout on a large scale for a medication that's used, that's a very small use drug like a fentanyl for breakthrough pain or some of the other drugs that have highly restrictive REMS.

I think that it might create a system where the whole system doesn't work and just breaks down and the drug just goes away. We were asked, as number C, as unique programs, a program that seems to work -- there's a lot of evidence that continuing education for physicians doesn't work unless there's post-tests and practice change. At least that's what you have to document to get CMEs approved.

That being the case, a program like is being used for Suboxone seems to be the physician is guaranteed to be educated, and I don't know what's

being planned for the class REMS, but it seems like the physician is being educated. There are watchdog agencies looking over people's shoulders, especially if it's in a state with a pharmacy registry.

I'm just wondering if there isn't a -- and we also have to consider there are resource questions, and this does not sound like an inexpensive program to run, and knowing what the cost of branded long-acting pain medication is, adding it on top of that could make it prohibitive for a large number of people.

So I think we have to -- while, like I say, there's an instinct to want to have the safest approach, I want to be resource-conservative and practical in what might work the best.

DR. KIRSCH: Dr. Zito?

DR. ZITO: I wanted to go back to a point that Dr. Jenkins raised a few minutes ago to help me understand. When you say Exalgo and Embeda carry the same risks, I'm wondering, does crushed Exalgo carry the same risk as crushed Embeda or any of the other crushable products that abusers might have access to?

DR. KIRSCH: Dr. Hertz?

DR. HERTZ: Based on the information we have, crushed Embeda and crushed Exalgo will both release their drug without the extended release characteristics.

DR. ZITO: So you're making a negative safety statement, not a positive one. Is that what I should deduce?

DR. HERTZ: Neither has physical properties intended to make them more difficult to crush.

DR. ZITO: So they're both increased risk for abusive use. They both have a similar risk.

DR. HERTZ: All of the extended release products right now will release their drug substance when physically manipulated to do so.

DR. ZITO: So the presence of the antagonist doesn't mitigate the risk.

DR. HERTZ: The antagonist is dosed such that it's intended to interfere with the high, but it's not sufficient to reverse an overdose or prevent an overdose in Embeda.

DR. KIRSCH: Dr. Markman?

DR. MARKMAN: I just have a follow-up on

that question. Do you think that would have any effect on behavioral reinforcement if you were to crush it repeatedly? To answer Dr. Zito's question, I think that's the question Dr. Zito is asking.

DR. HERTZ: The information in the label suggests that in some individuals, it will; in many, it will not. That's why it also says that there's no evidence that the product can deter abuse in the label. Is that not clear? Do you need more information?

DR. KIRSCH: Dr. Zito?

DR. ZITO: Not for the moment.

DR. KIRSCH: Dr. Markman, do you have another question?

DR. MARKMAN: I was going to attempt to respond to Dr. Jenkins' query, if that's appropriate now.

DR. KIRSCH: Yes.

DR. MARKMAN: And I think Dr. Zito gets to this point. With regard to the question you posed of risk versus benefit, I think, for myself, as a clinician, one of the most challenging parts of pain

management for chronic pain is to weigh the risk-benefit assessment of any particular treatment decision.

What makes your question so challenging is you're sort of asking us to do that in a drug-specific way across a very large population. I realize that's the charge you've been tasked with, and I'm empathetic to that.

But again, the hardest part of pain management or one of the hardest parts is treatment matching, assessing risk and benefit, and I do think that there are specific subpopulations where that risk-benefit profile is different, and those different populations are candidates to receive this drug.

Dr. Lorenz talked about one of those populations, patients with cancer, where I think the risk-benefit profile is, obviously, far more in favor of patients with cancer pain. But there are certainly many populations of patients with non-cancer pain for whom I think the similar claim could be made.

That being said, I believe that Embeda is also a unique submission, a unique compound which has

its own risk-benefit profile which is different from that of this drug. For that reason, I think this needs a program unto itself.

I recognize, from an administrative standpoint, that's a challenge, but I think it's one worth taking, and the reason I think it's worth it is because of Dr. Deshpande's point, which is that the last thing I think that any of us wants to do is have a drug be introduced in such a way so that down the road, it's not going to be available, because we do think there is a potential benefit here.

So to have it rolled out in such a way that unintended consequences ultimately have it being pulled from the market is the least desirable outcome, from my standpoint. So the goal here is to get this drug to the population of patients who are most likely to benefit and to secure that over the long term.

I think that that was a point made by the sponsor this morning when talking about how their commercial representatives would approach this. They, too, have a stake in making this be as safe as possible so that benefit can be enjoyed by as many

patients as possible.

So I think that's the argument here, to do the rollout, as Dr. Morrato was saying, in such a way that we optimize that risk-benefit ratio not just over six months or one year, but over what hopefully will be decades.

DR. KIRSCH: Dr. Flick? Dr. Rappaport?

DR. RAPPAPORT: Can I just respond to that quickly? I want to clarify one point, which is that the company can institute their program as it stands without our requiring it.

I just want to add that into your thinking, because if they do something, any type of program that they want, and we don't require quite an extensive program, we can see how it works and whether we need to require something like that over time by collecting new safety information, new problems occurring. So I just want to throw that in there as an option.

DR. KIRSCH: Dr. Flick?

DR. FLICK: I just want to clarify. If the sponsor adopts this program, as they've outlined, and FDA comes out with a different program later that has

different aspects, will the sponsor be asked to adopt the new program, stay with the same program or integrate the two programs?

DR. JENKINS: I think some of that depends upon our understanding of the risk of this product versus the risk of the other group in the class of extended release and the methadone for pain.

If we come to the conclusion that the risk is greater here and that the restrictions need to be greater to ensure that the benefits outweigh the risks, then they may continue to have a unique program.

The FDAAA statute actually encourages FDA to, wherever possible, limit the burden on the health care system and ensure that the restrictions we put in place are necessary and commensurate to ensure that the benefits of the drug exceed the risks.

So that's why, for the class, we didn't want to have an OxyContin program, an Embeda program, every one of the different products and every generic having a different program. We want to have one program that covers that whole class.

We're trying to decide and asking you to help us decide should Exalgo go in that program or should it stand alone. For Embeda, as implied by the title of the slide, they have an interim REMS and they've been told very clearly that when we develop the class REMS, if it's more restrictive than their interim REMS, they will be expected to adopt the new class REMS.

I can't say yet what the class REMS is going to be, not because I can't tell you, but just because we haven't developed it yet. If Exalgo gets a more restrictive program, and later we develop a less restrictive program for the class, but you convince us that there's a reason that Exalgo needs a more restrictive program, they may continue to stand alone.

DR. FLICK: From the standpoint of a prescriber, it would seem to me that we want to avoid having separate programs because of the burden on the patient and the prescriber.

From a public health standpoint, it concerns me that we have a system in which the burden of oversight is left to the sponsor, and that we are --

if one reads the remarks by the sponsor, there are many incentives for the sponsor to not undertake close oversight, and there are very few incentives for the sponsor to be careful in their oversight. And it would seem to me, regardless of what program is established, that there must be some external oversight to that program.

DR. JENKINS: Can I respond to that? Just to be clear, we regulate the sponsor, and whatever REMS we determine is required, that is an enforceable program, where the sponsor is required to make sure that that program is put into place.

They are required to assess the success of the program and submit those to us on a periodic basis. If they fail to implement the program, the statute makes available penalties that the FDA can impose, ranging from civil money penalties, dollar amounts that they can be fined for failure, all the way up to withdrawal of the drug from the market.

So there are significant incentives in the statute for the companies to comply with these REMS programs, and the oversight is the FDA, because we're

in charge of determining exactly what the program will be. We review all the documents, all the materials. We approve every aspect of the program. Then we expect the sponsor to implement it and provide us with information, and if they're not doing what they're required to do, there are significant penalties.

So I think FDA is the oversight, the external oversight that you're calling for. I think that's the role of the FDA, that Congress charged us with that task, and I think sponsors take these programs very seriously, because they don't want to fail on a REMS not only because of the liability of what we can do to them, but also just liability in general.

DR. KIRSCH: Dr. Vaida?

DR. VAIDA: In follow-up with what Dr. Flick was just saying and for Dr. Jenkins, if I understand it correctly, then, like after a six-month period, let's say, if we said for the company to put in their REMS what they suggested for this product, and after six months, the FDA would get that data and evaluate to make sure that they're not only following it, but

in follow-up to how closely they're following it.

If they say, "well, we've had 2,000 prescribers sign up," but we all know that there's been hundreds of thousands of prescriptions written and they said, "well, those just didn't want to sign," the FDA does have something to come back with to say this isn't good enough.

DR. JENKINS: Yes. Whatever program we require, they are required to do assessments and submit data to us to assess how effective have they been in actually implementing the program and is the program achieving the goals that were established.

These programs have goals that we articulate in the REMS. Now, obviously, six months into the program is early to be completely assessing the success, because it's going to take time for these things to get rolled out and up and running.

But the example you have seen is we have asked for assessment as early as six months so that we can make sure that they are doing the administrative part and we can start gathering the data.

The example you gave, if they've only

enrolled 2,000 prescribers and there have been way more prescriptions than their prescribers are prescribing and pharmacies that are dispensing that aren't enrolled in the program, then they clearly aren't meeting the terms of the REMS and the sponsor can be held responsible for that through enforcement action, as I described earlier.

We have independent mechanisms also available to us to validate the information they provide us. So if a sponsor came back and said, "we've only enrolled 2,000 prescribers and those are the only people that are prescribing the medication," we have independent ways of assessing who actually are prescribing drugs and we can match that up.

So I guess it was Ronald Reagan who said "trust, but verify," and our job is to verify that what we're being told is accurate, and we have independent means of doing that in addition to what they provide us.

DR. KIRSCH: Dr. Morrato?

DR. MORRATO: It seems that what you're asking then is if there's a point of differentiation

between Exalgo and Embeda that would justify a different level of REMS.

One thing I noticed was that Exalgo is for opioid-tolerant patients. Is Embeda indicated that way?

DR. HERTZ: Only the higher doses.

DR. MORRATO: And for the class labeling that's under discussion, is that part of the discussion as it relates to whether it's opioid-tolerant or not and any differentiation of the type of program?

DR. HERTZ: No. Several products have dosing instructions and warnings that the higher doses are intended only for opioid-tolerant patients, but the lower doses are for the discretion of the prescriber.

DR. MORRATO: So start there, titrate up.

DR. RAPPAPORT: Just to clarify, somebody else was talking about this earlier, most people in the field use the cutoff of 60 milligrams of morphine equivalence as being opioid-tolerant for at last a week or two.

So wherever that falls in terms of the particular drug, so for OxyContin, it may be about the same, a little bit different, where, here, all of the doses that are available are above that cutoff point. So that's what we use. It's just a matter of -- the reason is just to make sure the people getting over 60 milligrams morphine equivalence are considered opioid-tolerant.

DR. MORRATO: So I just was clarifying, but that was the point that I wanted to make, is that that's a point of differentiation with this drug compared to others; that you're assuming that there's a prior drug history that the patient has gotten to a certain level of drug need before they're using this drug. They're not just starting out with it. Is that correct?

DR. RAPPAPORT: For all of the doses of this drug, but for many of the doses of other drugs in the class.

DR. MORRATO: I guess I'm just trying to say I think I think that may be a point of differentiation, why you would launch Exalgo

differently than you would another one, such as Embeda.

Just to reiterate what we have talked, you have a critical window in which you do the launch right once and you set it on its trajectory, and if you aren't careful during that window, for all the reasons that have been mentioned, I think it's easier to scale back a program than it is to get one to two years in and you see what the class REMS are turning out like and you're scaling up. I think it makes it messier.

It may be more of a burden initially, but I think you can construct it in such a way that you're targeting the patients where there's the greatest need and, therefore, the greatest opportunity for benefit as part of it.

DR. KIRSCH: Dr. Deshpande?

DR. DESHPANDE: I think I agree with Dr. Morrato, but I'm not going to be as eloquent. What I heard from Dr. Jenkins' comments was for us to consider whether this formulation in this medication is more dangerous or as dangerous as the others in the

extended release class.

To me, if they were all packaged in equipotent doses, in little pills, then we can say that this is the same class of medications. Think of it even more simply than that. Am I more concerned about hydromorphone use than about morphine use, from the safety and comfort and thinking about public health standpoint?

I'm more concerned about hydromorphone than I am about morphine. That drives the decision to say, well, this is not like the rest of the extended release drugs, and that's the reason to think about what we need a different REMS and a different rollout, as you're pointing out.

DR. KIRSCH: The last comment is Dr. Markman.

DR. MARKMAN: I would agree. I think this is a unique compound. I also just want to follow-up on an earlier point, also. In the marketplace, in reality, for folks who are prescribing these medications, there are a lot of other filters to control prescribing, and because this is going to be a

new entrant opioid which is a branded product, in a world where the options are -- there are many generic options or at least several generic options, another mechanism through which physicians are commonly having their decisions modulated is that of prior authorization.

So the reality is that in the prior authorization process, when you write this prescription, you will receive a fax from the pharmacy immediately, and many of these questions that are built into most of these programs will be asked of you by the company or the concern that's paying for that.

So that is just to understand that in reality, when you're prescribing those medications, a new branded medication such as this one, which will likely be priced differently than the generic options, there will be other filters in place.

DR. KIRSCH: Dr. Flick has, I guess, the last word.

DR. FLICK: I think we're being asked to decide whether we need a special REMS for this product. One of Dr. Jenkins' comments was that the

sponsor can volunteer to do something different than what FDA may suggest. I wonder if the sponsor would like to comment on their willingness to do that.

DR. KIRSCH: Yes, sponsor, please.

DR. NEUMAN: When we designed the Exalgo Alliance, it was our best effort to try to decide what is the appropriate balance between risk and access, and we always designed it to be flexible.

We also recognized that there is more than one way to get there. We never thought that the Exalgo Alliance, the way it was written, had to be the way to do it. That was just our best reasoning at the time it was created.

To get to the better way, I think, is around a dialogue. And to clarify my earlier point, we are committing to having an external advisory board in place prior to the launch of the Exalgo product itself into the marketplace.

I think what you hear today mimics the fact that it was very difficult to strike this balance. So my answer to your question is it depends. What we want to do is have a dialogue with our external

advisory board, that admittedly is not constituted yet, but coming, but also have a dialogue with the agency and see what the best mix is.

I will tell you that nothing is off the table, and that if it is appropriate, we will add features that may not be required by the agency. But it's really not appropriate for me to say now definitely yes or no until I've had the input of other groups that have different perspectives.

DR. KIRSCH: Thank you. So it's now my job to try to summarize the comments based on this question. The discussion, I think, is very healthy. What I heard -- and, again, I'm happy to be edited if you all have a different assessment -- is that the Committee is endorsing the REMS program as outlined by the sponsor, with one caveat, that it be done in a phased-in fashion, looking primarily at particular practitioner types, provider types, and particular patient disease types so that this potentially very valuable drug in the market -- gets put into the market in a way that will allow it to have a sustained presence.

Comments for edit? Oh, my gosh. So I think we've done our job, unless FDA has other things for us to address.

DR. RAPPAPORT: No. I think we found the discussion this afternoon very useful. We appreciate your taking your time to do this, and we don't have any other questions right now.

DR. KIRSCH: I'd like to thank the members of the Committee and I'd also like to thank the sponsor, FDA, and of course, our patients who testified on behalf of this topic. Thank you for your help.

[Whereupon, at 3:13 p.m., the meeting was concluded.]